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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TSUTSUMI, Hideo [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). AKAHANE, Atsushi [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(74) Agent: TAKASHIMA, Hajime; Fujimura Yamato Seimei Bldg., 2-14, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0044 (JP).

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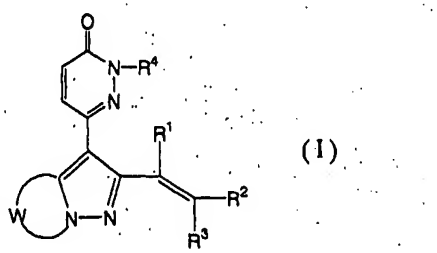
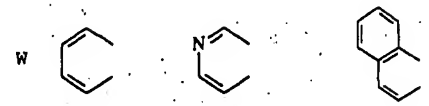
(54) Title: PYRIDAZINONE COMPOUND AS ADENOSINE ANTAGONISTS



(I)



(57) Abstract: A compound of the following formula (I): wherein R^1, R^2, R^3 and R^4 are each independently hydrogen or a suitable substituent, in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12) which is optionally interrupted by heteroatom(s) and optionally having suitable substituent(s); andW is , or ,or a salt thereof.The compound of the above formula (I) and a salt thereof are adenosine antagonists and are useful as medicaments.

WO 03/004494 A1

DESCRIPTION

PYRIDAZINONE COMPOUNDS AS ADENOSINE ANTAGONISTS

TECHNICAL FIELD

The present invention relates to a novel pyridazinone compound, preferably a pyrazolopyridinyl pyridazinone compound, and a salt thereof, which are useful as medicaments..

BACKGROUND ART

Some pyrazolopyridinyl pyridazinone compounds to be useful as remedy for renal failure, heart failure, depression and the like are known (e.g. WO 95/18128, WO 98/03507, WO 00/24742, etc.).

DISCLOSURE OF THE INVENTION

The present invention relates to a novel pyridazinone compound, preferably a pyrazolopyridinyl pyridazinone compound, and a pharmaceutically acceptable salt thereof, which are useful as medicaments; processes for the preparation of said pyridazinone compound and a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising, as an active ingredient, said pyridazinone compound or a pharmaceutically acceptable salt thereof; a use of said pyridazinone compound or a pharmaceutically acceptable salt thereof as a medicament; and a method for using said pyridazinone compound or a pharmaceutically acceptable salt thereof for therapeutic purposes, which comprises administering said pyridazinone compound or a pharmaceutically acceptable salt thereof to a human being or an animal.

The pyridazinone compound and a salt thereof are adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and possess various pharmacological actions such as anticatalepsy action, cognitive enhancing action, analgesic action, locomotor action, antidepressant action, diuretic action,

cardioprotective action, cardiotonic action, vasodilating action (e.g. cerebral vasodilating action, etc.), the action of increasing the renal blood flow, renal protective action, improvement action of renal function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin release, the action of increasing the production of erythropoietin, inhibiting action of platelet aggregation, and the like.

They are useful as cognitive enhancer, antianxiety drug, antidementia drug, psychostimulant, analgesic, cardioprotective agent, antidepressant, ameliorants of cerebral circulation, tranquilizer, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal failure (renal insufficiency), drug for renal toxicity, renal protective agent, drug for improvement of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilator, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppressive action of adenosine, antidiabetic agent, drug for ulcer, drug for pancreatitis, drug for Meniere's syndrome, drug for anemia; drug for thrombosis, drug for myocardial infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, drug for angina pectoris, and the like;

and useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure;

hypertension (e.g. essential hypertension, nephrogenous hypertension, etc.);

circulatory insufficiency (acute circulatory insufficiency) caused by, for example, ischemia/reperfusion injury (e.g.

myocardial ischemia/reperfusion injury, cerebral ischemia/reperfusion injury, peripheral ischemia/reperfusion injury, etc.), shock (e.g. endotoxin shock, hemorrhagic shock, etc.), surgical procedure, and the like; post-resuscitation asystole;

bradyarrhythmia;

electro-mechanical dissociation;

hemodynamic collapse;

SIRS (systemic inflammatory response syndrome);

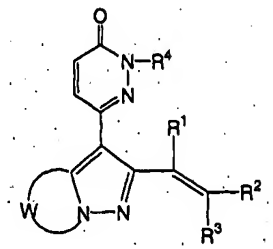
multiple organ failure;

renal failure (renal insufficiency) (e.g. acute renal failure, etc.), renal toxicity [e.g. renal toxicity induced by a drug such as cisplatins, gentamicin, FR-900506 (disclosed in EP0184162), cyclosporin (e.g. cyclosporin A) and the like; glycerol, etc.], nephrosis, nephritis, edema (e.g. cardiac edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, carcinomatous ascites, gestational edema, etc.);

obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer such as peptic ulcer (e.g. gastric ulcer, duodenal ulcer, etc.), pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus (e.g. mechanical ileus, adynamic ileus, etc.); and myocardial infarction, thrombosis (e.g. arterial thrombosis, cerebral thrombosis, etc.), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, and the like.

The present invention can provide a novel compound represented by the following formula (I) and (I').

[1] A compound of the following formula (I):

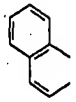


(I)

wherein

R^1, R^2, R^3 and R^4 are each independently hydrogen or a suitable substituent,

in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12) which is optionally interrupted by heteroatom(s) and optionally having suitable substituent(s); and

W is  ,  or  ,

or a salt thereof.

[2] The compound of the above-mentioned [1], wherein

R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxy(lower)alkyl, cycloalkyl, acyl, aryl or heteroaryl,

in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12), at least one CH_2 of which is(are) optionally replaced by O, S, SO_2 or optionally protected imino, and optionally having suitable substituent(s), or

R^2 and R^3 together may form bicycloalkylidene or tricycloalkylidene; and

R^4 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkadiynyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl(lower)alkyl, heterocyclic(lower)alkyl, lower alkoxy(lower)alkyl or acyl(lower)alkyl,

or a salt thereof.

[3] The compound of the above-mentioned [2], wherein

R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxymethyl, cycloalkyl, acetyl, phenyl, benzodioxanyl, indolyl optionally having lower alkyl, quinolyl or morpholinophenyl,

in which R^1 and R^2 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 10, one CH_2 of which is optionally replaced by O or S and optionally having lower alkyl),

in which R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 3 to 12, at least one CH_2 is(are) optionally replaced by O, S, SO_2, NH, $N(COCH_3)$ or NBoc and optionally having lower alkyl), bicycloalkylidene or tricycloalkylidene; and

R^4 is lower alkyl, lower alkenyl, lower alkynyl, lower alkadiynyl, lower cycloalkyl, lower cycloalkyl(lower)alkyl, phenyl(lower)alkyl, dioxolanyl(lower)alkyl, oxadiazolyl(lower)alkyl, lower alkoxy(lower)alkyl, lower alkanoyl(lower)alkyl, lower alkoxycarbonyl(lower)alkyl, or a salt thereof.

[4] The compound of the above-mentioned [3], wherein

R^1 and R^2 are each independently hydrogen or lower alkyl,

in which R^1 and R^2 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 10, one CH_2 of which is optionally replaced by O or S and optionally having lower alkyl);

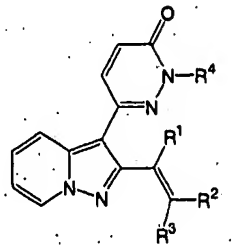
R^3 is hydrogen, lower alkyl, hydroxymethyl, cycloalkyl, acetyl, phenyl, benzodioxanyl, indolyl optionally having lower alkyl, quinolyl or morpholinophenyl,

in which R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 3 to 12, at least one CH_2 of which is(are) optionally replaced by O, S, SO_2, NH, $N(COCH_3)$ or NBoc and optionally having lower alkyl), bicycloheptylidene or tricyclodecylidene;

R^4 is methyl, ethyl, propyl, isopropyl, allyl, propynyl,

ethynylbutynyl, cyclopropylmethyl, benzyl, dioxolanylmethyl, oxadiazolylmethyl, methoxyethyl, acetonyl or methoxycarbonylmethyl,
or a salt thereof.

[5] The compound of the above-mentioned [1] represented by the following formula (I'):



(I')

wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen or a suitable substituent,
in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12), which is optionally interrupted by heteroatom(s) and optionally having suitable substituent(s);
or a salt thereof.

[6] The compound of the above-mentioned [5], wherein
R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxy(lower)alkyl, cycloalkyl, acyl, aryl or heteroaryl,
in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12), at least one CH_2 of which is optionally replaced by O, S, SO_2 or optionally protected imino,
and optionally having suitable substituent(s), or
R^2 and R^3 together may form bicycloalkylidene or tricycloalkylidene; and
R^4 is hydrogen, lower alkyl, cycloalkyl or cycloalkyl(lower)alkyl whose CH_2 is optionally replaced by O,

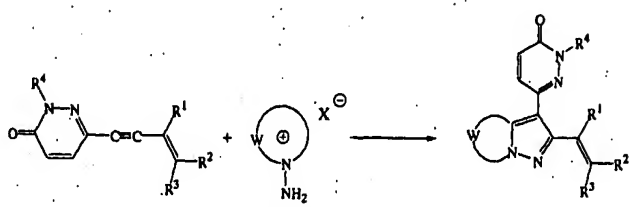
NH, S or SO_2,
or a salt thereof.

[7] The compound of the above-mentioned [6], wherein
R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxymethyl, cycloalkyl, acetyl, phenyl, benzodioxanyl, indolyl optionally having lower alkyl, quinolyl or morpholinophenyl,
in which R^1 and R^2 together may form $-(CH_2)_n-$ (wherein n is an integer of 2 to 6, and one CH_2 of which is optionally replaced by O or S and optionally having lower alkyl), or
in which R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 3 to 7, and at least one CH_2 of which is optionally replaced by O, S, SO_2, NH, $N(COCH_3)$ or NBoc and optionally having lower alkyl), bicycloalkylidene or tricycloalkylidene; and
R^4 is isopropyl,
or a salt thereof.

The present invention also provides a pharmaceutical composition comprising the above-mentioned compound of formula (I) or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

The object compound (I) and a salt thereof of the present invention can be prepared by the following processes.

Process 1

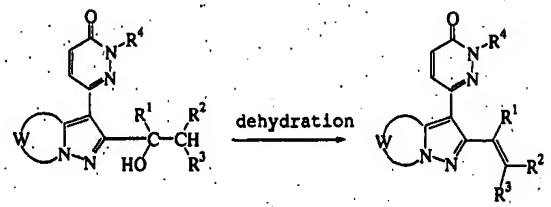


(I-a) (I-b) (I) or a salt thereof

wherein

R^1, R^2, R^3, R^4 and W are as defined above, and X is halogen.

Process 2



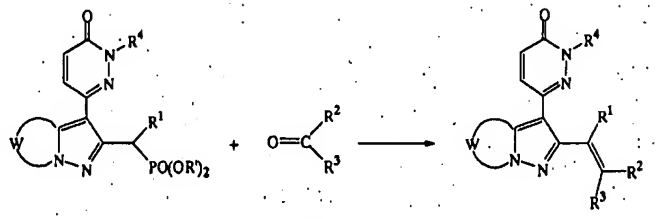
(2-a)

(I)
or a salt thereof

wherein

R^1, R^2, R^3, R^4 and W are as defined above.

Process 3



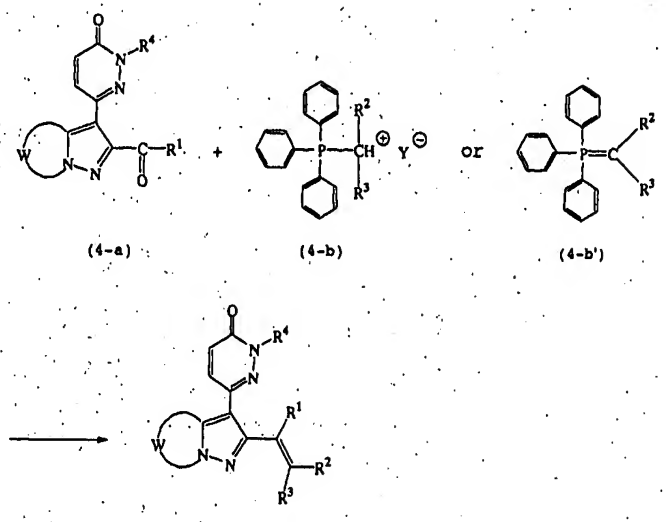
(3-a) (3-b)

(I)
or a salt thereof

wherein

R^1, R^2, R^3, R^4 and W are as defined above, and R' is lower alkyl.

Process 4



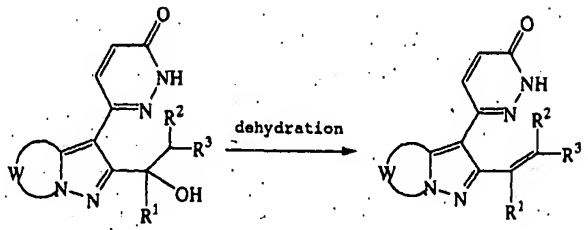
(4-a) (4-b) (4-b')

(I)
or a salt thereof

wherein

R^1, R^2, R^3, R^4 and W are as defined above, and Y is halogen.

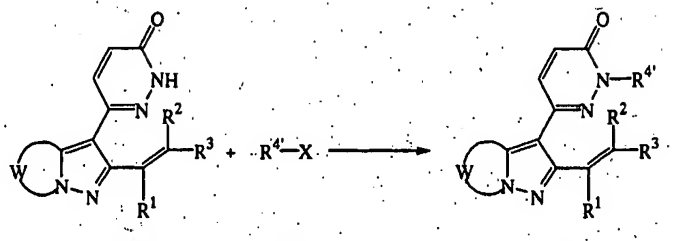
Process 5



(2-a') (I'-5)
or a salt thereof

wherein R^1, R^2, R^3 and W are as defined above.

Process 6



(I'-5) or a salt thereof (6-a) (I'-6) or a salt thereof

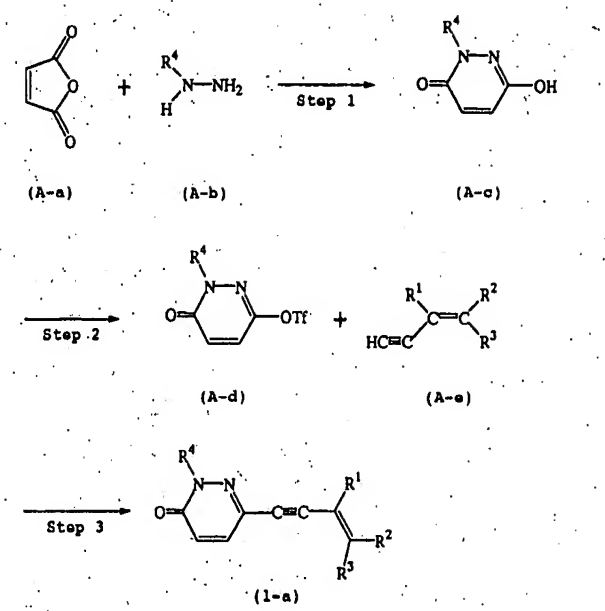
wherein

R^1, R^2, R^3, W and X are as defined above, and

$R^{4'}$ is a suitable substituent.

The starting compounds (1-a), (2-a), (3-a), (4-a) and (2-a') or a salt thereof are novel and can be prepared by the following processes.

Process A

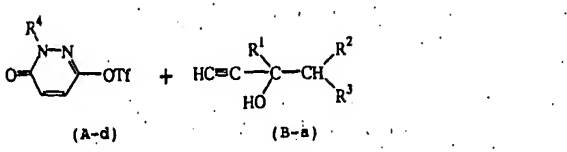


(A-a) (A-b) (A-c) (A-d) (A-e) (1-a)

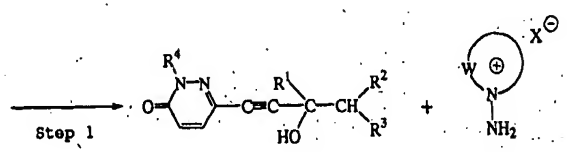
wherein

R^1, R^2, R^3 and R^4 are as defined above, and Tf is trifluoromethanesulfonyl group. The compound obtained in this process is used in Process 1.

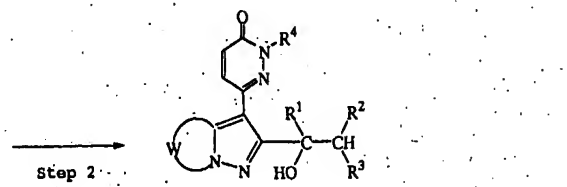
Process B



(A-d) (B-a)



Step 1 (B-b) (1-b)

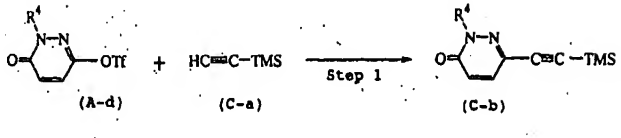


Step 2 (2-a)

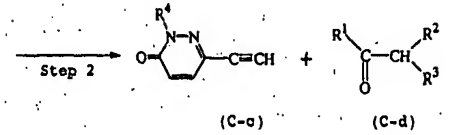
wherein

R, R^1, R^2, R^3, R^4, W and Tf are as defined above. The compound obtained in this process is used in Process 2.

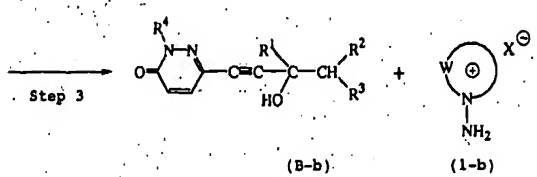
Process C



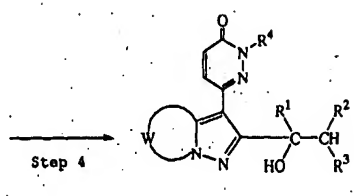
(A-d) (C-a) Step 1 (C-b)



Step 2 (C-c) (C-d)



Step 3 (B-b) (1-b)

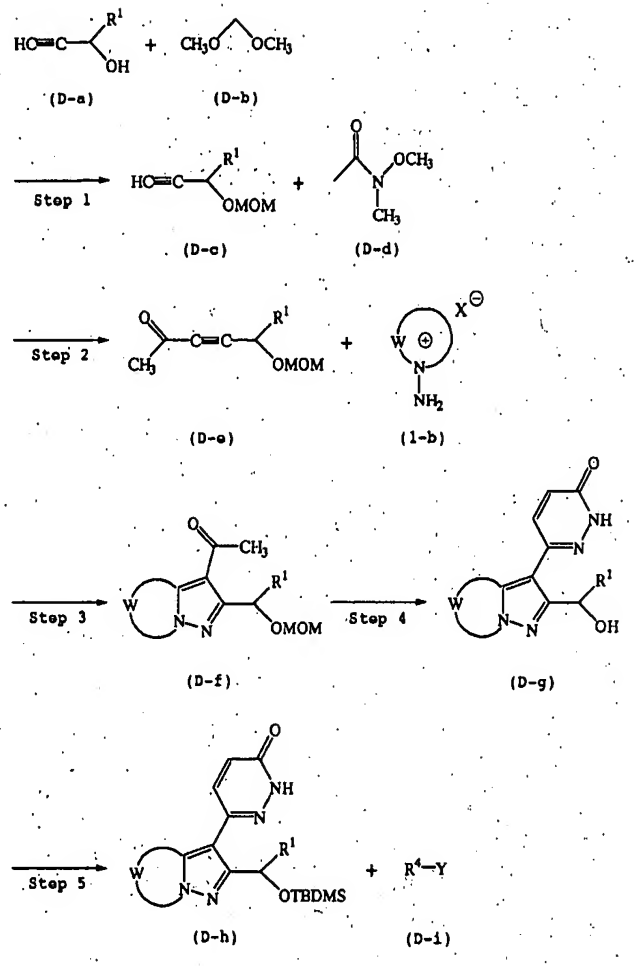


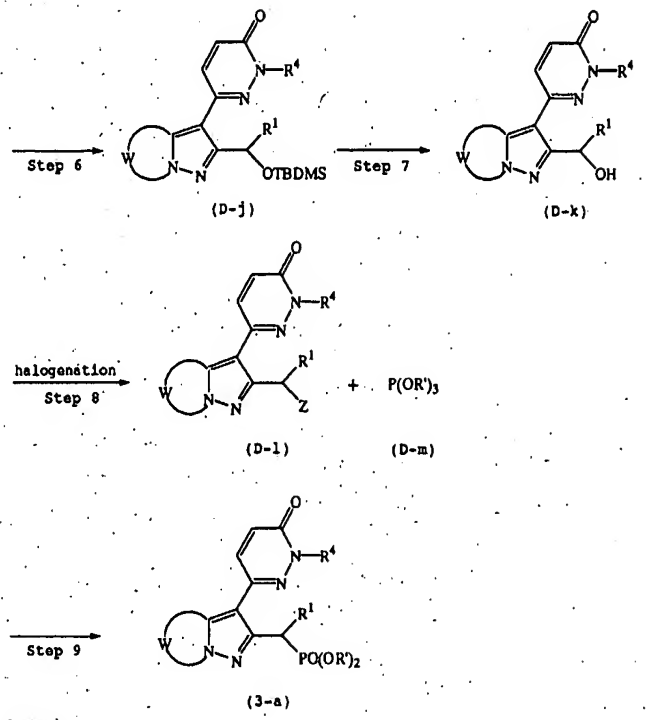
Step 4 (2-a)

wherein

R^1, R^2, R^3, R^4, W and X and Tf are as defined above, and TMS is trimethylsilyl group. The compound obtained in this process is used in Process 2.

Process D

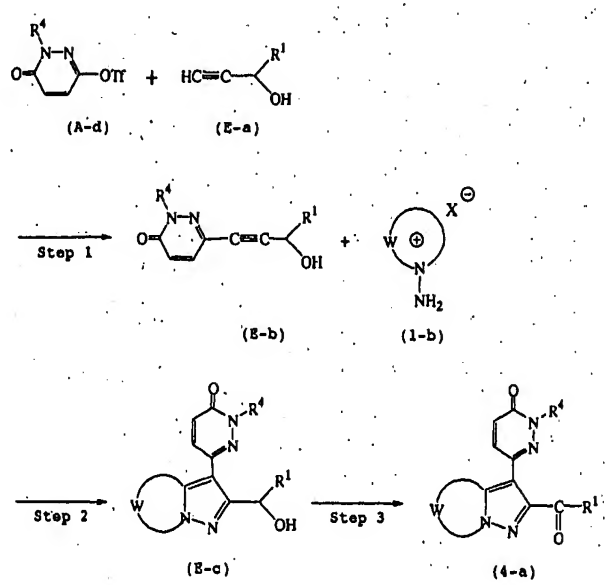




wherein

R^1, R^2, R^3, R^4, R' and W are as defined above, X, Y and Z are independently halogen, OMOM is methoxymethoxy group, and OTBDMS is (tert-butyldimethylsilyl)oxy group. The compound obtained in this process is used in Process 3.

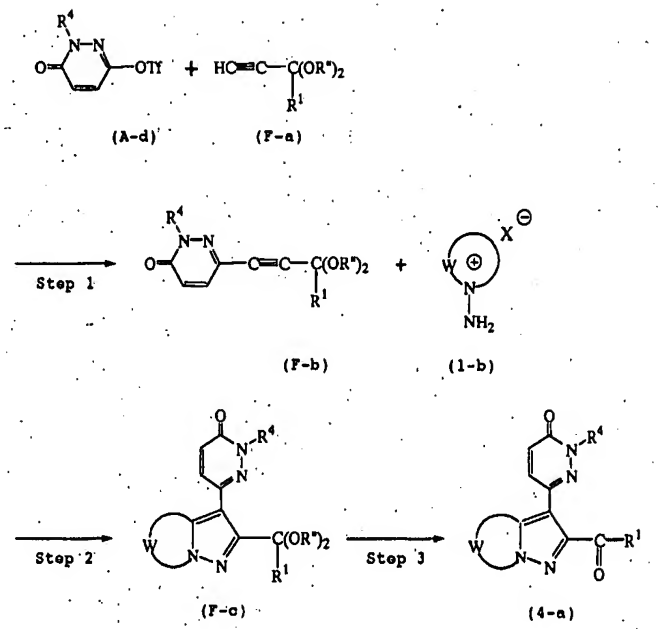
Process E



wherein

R^1, R^2, R^3, R^4, W and X are as defined above. The compound obtained in this process is used in Process 4.

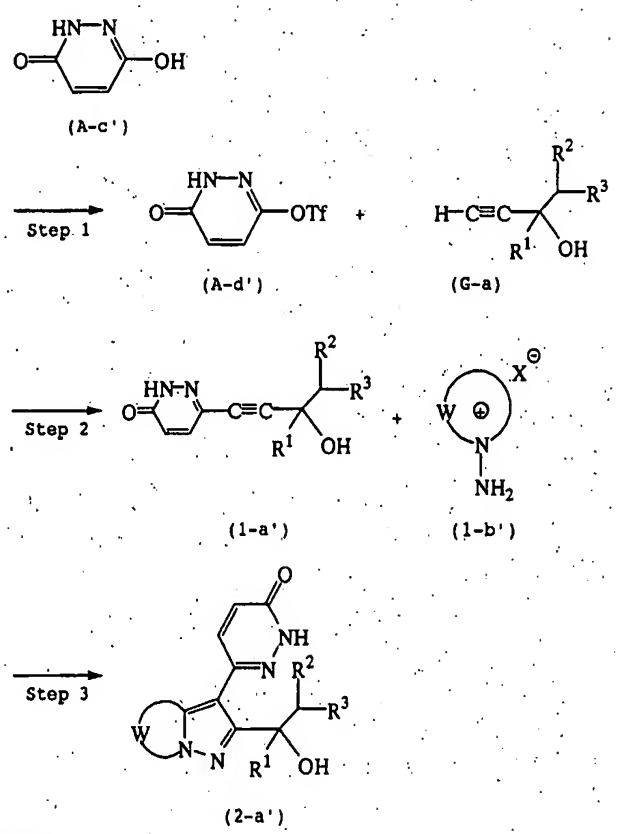
Process F



wherein

R^1, R^2, R^3, R^4, W, Tf and X are as defined above, and R″ is lower alkyl. The compound obtained in this process is used in Process 4.

Process G



wherein

R^1, R^2, R^3, W, Tf and X are as defined above, and R'' is lower alkyl. The compound obtained in this process is used in Process 5.

In the above-mentioned processes, the starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto.

The object compound (I) and a salt thereof can be prepared, for example, according to the methods as shown in the Preparations and Examples, or in a manner similar thereto.

The object compound (I) and a salt thereof may be further converted to the object compound (I) having another structure, for example, according to the procedures as illustrated in Examples 50, 51, 52 and 53, or in a manner similar thereto, or in a manner known in the art.

It is to be noted that the object compound (I) may include the geometrical isomer(s) due to the double bond(s) and/or the stereo isomer(s) due to the asymmetric carbon atom(s). In this regard, the isomer(s) can be converted to different isomer(s) according to a conventional method known in the art.

It is also noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

Suitable salts of the object compound (I) are conventional pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumalate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc.), a salt with amino acid (e.g. arginine, aspartic acid,

glutamic acid, etc.), and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms "cycloalkyl(lower)alkyl", "hydroxy(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, and the like, in which the preferred one is alkyl having 1 to 4 carbon atom(s), and the most preferred one is methyl, ethyl or isopropyl.

Suitable "cycloalkyl" and "cycloalkyl" moiety in the terms "cycloalkyl(lower)alkyl", may include cycloalkyl having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, in which the preferred one is cyclopropyl or cyclohexyl.

Suitable "cycloalkyl(lower)alkyl" may include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, and the like.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, and the like, in which the preferred one is hydroxymethyl.

Suitable "acyl" may include lower alkanoyl such as formyl, acetyl, propionyl, butyryl, isobutyryl, and the like; carboxy; protected carboxy (e.g. methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, and the like), and the like, in which the preferred one is acetyl.

Suitable "acyl(lower)alkyl" may include, lower

alkanoyl(lower)alkyl (e.g. acetylmethyl (acetonyl), acetylethyl, acetylpropyl, acetylisopropyl, acetylbutyl, acetylisobutyl, acetyl t-butyl, and the like), lower alkylcarbonyl(lower)alkyl (e.g. ethylcarbonylmethyl, ethylcarbonylethyl, ethylcarbonylpropyl, ethylcarbonylbutyl, propylcarbonylmethyl, propylcarbonylethyl, propylcarbonylpropyl, propylcarbonylbutyl, butylcarbonylmethyl, butylcarbonylethyl, butylcarbonylpropyl, butylcarbonylbutyl, and the like), lower alkoxycarbonyl(lower)alkyl (e.g. methoxycarbonylmethyl, methoxycarbonylethyl, methoxycarbonylpropyl, methoxycarbonylbutyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, ethoxycarbonylpropyl, ethoxycarbonylbutyl, propoxycarbonylmethyl, propoxycarbonylethyl, propoxycarbonylpropyl, propoxycarbonylbutyl, butoxycarbonylmethyl, butoxycarbonylethyl, butoxycarbonylpropyl, butoxycarbonylbutyl, and the like), and the like, in which the preferred one is methoxycarbonylmethyl.

Suitable "aryl" may include phenyl, tolyl, xylyl, naphtyl, and the like, in which the preferred one is phenyl.

Suitable "heteroaryl" may include heteroaryl containing at least one heteroatom selected from sulfur atom, oxygen atom and nitrogen atom, in which the preferred one is indolyl, quinolyl, benzodioxanyl or morpholinophenyl.

Suitable examples of "$-(CH_2)_n-$ (wherein n is an integer of 1 to 12) which is optionally interrupted by heteroatom(s)" may include $-(CH_2)_n-$, at least one CH_2 of which is optionally replaced by O, S, SO_2, NH, protected imino [e.g. $N(COCH_3)$, NBoc, and the like, wherein Boc is tert-butoxycarbonyl], and the like. The preffered one, among them, may be methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, $-CH_2-O-CH_2-$, $-CH_2-O-(CH_2)_2-$, $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-O-CH_2-O-CH_2-$, $-CH_2-S-CH_2-$, $-CH_2-S-(CH_2)_2-$, $-(CH_2)_2-S-(CH_2)_2-$, $-(CH_2)_2-SO_2-(CH_2)_2-$, $-(CH_2)_2-NH-(CH_2)_2-$, -

$(CH_2)_2$-N($COCH_3$)-$(CH_2)_2$-, -$(CH_2)_2$-N(Boc)-$(CH_2)_2$-, and the like.

The "-$(CH_2)_n$- which is optionally interrupted by heteroatom(s)" mentioned above may have one or more (preferably 1 through 3) suitable substituent(s) such as lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, and the like), and the like, in which the preffered one is methyl, and which may make bridge(s) to form bicyclic or tricyclic ring such as bicycloalkylidene, tricycloalkylidene, and the like.

Suitable "bicycloalkylidene" may include bicycloalkylidene having 4 to 11 carbon atoms such as bicycloheptylidene (e.g. bicyclo[2.2.1]heptylidene), and the like, in which the preferred one is bicyclo[2.2.1]heptylidene.

Suitable "tricycloalkylidene" may include tricycloalkylidene having 7 to 14 carbon atoms such as tricyclodecylidene (e.g. tricyclo[$3.3.1.1^{3,7}$]decylidene), and the like, in which the preferred one is tricyclo[$3.3.1.1^{3,7}$]decylidene.

Suitable "halogen" includes fluorine, bromine, chlorine and iodine.

The Processes for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (1-a) with the compound (1-b) in the presence of base.

Suitable compound (1-b) for the reaction may be, for example, 1-aminopyridinium iodide. Suitable base for the reaction may be, for example, potassium carbonate.

The reaction is usually carried out in a suitable solvent.

The reaction temperature for the reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The object compound (I) and a salt thereof can be prepared, for example, according to the procedure as illustrated in Example 1.

Process 2

The object compound (I) or a salt thereof can be prepared by dehydrating the compound (2-a).

Suitable dehydration agent may be, for example, Nafion® NR50, methanesulfonic acid, and the like.

The reaction is usually carried out in a suitable solvent.

The reaction temperature for the reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The object compound (I) or a salt thereof can be prepared, for example, according to the procedures as illustrated in Examples 2, 6, 7, 21, 68, 69 and 70, etc.

Process 3

The object compound (I) or a salt thereof can be prepared by reacting the compound (3-a) with the compound (3-b) in the presence of alkaline metal hydride.

Suitable alkaline metal hydride for the reaction may be, for example, sodium hydride.

The reaction is usually carried out in a suitable solvent.

The reaction temperature for the reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The object compound (I) and a salt thereof can be prepared, for example, according to the procedure as illustrated in Example 23.

Process 4

The object compound (I) or a salt thereof can be prepared by reacting the compound (4-a) with the compound (4-b) or the compound (4-b').

The compound (4-b) suitable for this reaction may be, for example, methyltriphenylphosphonium bromide. When the

compound (4-b) is used, the reaction is conducted in the presence of alkoxide such as potassium t-butoxide.

The compound (4-b') suitable for this reaction may be, for example, 1-(triphenylphosphoranylidene)acetone.

This reaction is usually carried out in a suitable solvent.

The reaction temperature of this reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The object compound (I) and a salt thereof can be prepared, for example, according to the procedures as illustrated in Examples 48 and 49.

Process 5

The object compound (I'-5) or a salt thereof can be prepared by dehydrating the compound (2-a').

Suitable dehydration agent may be, for example, methanesulfonic acid, and the like.

The reaction is usually carried out in a suitable solvent.

The reaction temperature for the reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The object compound (I'-5) or a salt thereof can be prepared, for example, according to the procedures as illustrated in Example 54.

Process 6

The object compound (I'-6) or a salt thereof can be prepared by reacting the compound (I'-5) with the compound (6-a).

The reaction is usually carried out in a suitable solvent.

The reaction temperature for the reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The object compound (I'-6) or a salt thereof can be prepared, for example, according to the procedures as

illustrated in Example 55.

Process A

The compound (1-a) can be prepared according to the Steps 1 to 3 as illustrated above.

The compound (1-a) can be prepared, for example, according to the procedures as illustrated in Preparations 1, 2 and 3.

Process B

The compound (2-a) can be prepared according to the Steps 1 to 2 as illustrated above.

The compound (2-a) can be prepared, for example, according to the procedures as illustrated in Preparations 3 and 48.

Process C

The compound (2-a) can be prepared according to the Steps 1 to 4 as illustrated above.

The compound (2-a) can be prepared, for example, according to the procedures as illustrated in Preparations 32, 33, 34, 48, 76, 77 and 78.

Process D

The compound (3-a) can be prepared according to the Steps 1 to 9 as illustrated above.

Suitable halogenation agent used in Step 8 may include one, which can be applied to conversion of a hydroxy group to halo group, such as phosphorus halide (e.g. phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus tribromide, phosphorus pentabromide, etc.), thionyl halide (e.g. thionyl chloride, etc.), phosgene, and the like.

The reaction is usually carried out in a suitable solvent.

The reaction temperature of this reaction is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The compound (3-a') can be prepared, for example, according to the procedures as illustrated in Preparations

64, 65, 66, 67, 68, 69, 70, 71 and 72.

Process E

The compound (4-a) can be prepared according to the steps 1 to 3 as illustrated above.

The compound (4-a) can be prepared, for example, according to the procedures as illustrated in Preparations 7, 16 and 31.

Process F

The compound (4-a) can be prepared according to the steps 1 to 3 as illustrated above.

The compound (4-a) can be prepared, for example, according to the procedures as illustrated in Preparations 10, 21 and 30.

Process G

The compound (2-a') can be prepared according to the steps 1 to 3 as illustrated above.

The compound (2-a') can be prepared, for example, according to the procedures as illustrated in Preparations 73, 74 and 75.

The object compound (I) and a salt thereof of the present invention is an adenosine antagonist and possesses the various pharmacological actions as stated before.

In order to show the usefulness of the compound (I) of the present invention, the pharmacological test result of the representative compounds of the present invention is shown in the following.

Test 1: Adenosine antagonistic activity of the compound (I)

[I] Test method

The adenosine antagonistic activity [Ki (nM)] of the test compound was examined by radioligand binding techniques using 8-cyclopentyl-1,3-dipropylxanthine, [dipropyl-2,3-^{3}H(N)] ([^{3}H]DPCPX, 4.5 nM) for human A_1 receptor and [^{3}H]CGS 21680 (20 nM) for human A_{2a} receptor.

[II] Test compound

6-[2-(1-Cyclopenten-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (Example 5)

2-Isopropyl-6-{2-[(1E)-1-propenyl]pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone (Example 18)

2-Isopropyl-6-[2-(2-methyl-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (Example 19)

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(2-propynyl)-3(2H)-pyridazinone (Example 60)

[III] Test result

Table 1

Test compound (Example No.)	Adenosine Receptor Binding (Human) (Ki: nM)	
	A_1	A_{2a}
Example 5	0.19	1.92
Example 18	2.49	1.63
Example 19	0.33	0.45
Example 60	0.25	1.67

Test 2: Anticatalepsy activity in Mouse

[I] Test method

The test compound (3.2 mg/kg) was administered orally with ddY mice (n=7). Then, haloperidol (0.32 mg/kg) was injected intraperitoneally 30 min. after the administration of the compound. Thirty min. after the injection, the cataleptic responses of mice were measured. The forelimbs of each mouse were placed on a 3 cm high, 3 mm wide horizontal bar, and the duration of cataleptic posture was measured for up to 30 sec.

[II] Test compound

6-[2-(1-Cyclopenten-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (Example 5)

2-Isopropyl-6-{2-[(1E)-1-propenyl]pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone (Example 18)

2-Isopropyl-6-[2-(2-methyl-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (Example 19)

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(2-propynyl)-3(2H)-pyridazinone (Example 60)

[III] Test result

Table 2

Test compound (Example No.)	Manifestation rate of catalepsy in mouse (number of mouse)
Example 5	2/7
Example 18	3/7
Example 19	3/7
Example 60	1/7

The object compound (I) and a salt thereof of this invention are useful as adenosine antagonists (especially, A_1 receptor and A_2 (particularly A_{2a}) receptor dual antagonists) and for the prevention and/or the treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, and the like.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the object compound (I) or a salt thereof as an active ingredient in admixture with an organic or inorganic

carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. In addition, auxiliary, stabilizing agents, thickening agents, coloring agents and perfumes may be used where necessary. The object compound (I) or a salt thereof is included in a pharmaceutical composition in an amount sufficient to produce the desired above-mentioned pharmaceutical effect upon the process or condition of diseases.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous, intramuscular, pulmonary or oral administration, or insufflation. While the dosage of therapeutically effective amount of the object compound (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-100 mg of the pyridazinone compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.1-100 mg of the pyridazinone compound (I) per kg weight of a human being or an animal, and in case of oral administration, a daily dose of 0.5-100 mg of the pyridazinone compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the above-mentioned diseases.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a solution of maleic anhydride (41.57 g) in

glacial acetic acid (310 mL) was added 1-isopropylhydrazine (31.43 g) at ambient temperature. The mixture was heated under reflux for 5 hours and concentrated under reduced pressure to give a solid. The solid was triturated with isopropyl ether, collected by filtration, and recrystallized from a mixture of methanol and isopropyl ether to give 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (60.27 g).

mp: 162-164°C (methanol-isopropyl ether);

IR (KBr): 1504 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.22 (6H, d, J=6.66 Hz), 5.03 (1H, 7-plet, J=6.65 Hz), 6.85 (1H, d, J=9.62 Hz), 7.01 (1H, d, J=9.62 Hz), 10.95 (1H, br. s);

Mass (APCI): 155 $(M+H)^+$;

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17.
Found: C, 54.72; H, 6.61; N, 18.13.

Preparation 2

To a solution of 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (5.00 g) in pyridine (32 mL) was added dropwise trifluoromethanesulfonic anhydride (5.51 mL) under ice-cooling. The mixture was stirred under ice-cooling for one hour and at ambient temperature for 3 hours. Pyridine was removed under reduced pressure to give a residue. The residue was dissolved in a mixture of ethyl acetate and water. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 8:2 v/v) to give 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate as a solid (8.66 g).

mp: 45-46°C (hexane);

IR (KBr): 1660, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.34 (6H, d, J=6.62 Hz), 5.23 (1H, 7-plet, J=6.61 Hz), 7.04 (1H, d, J=9.83 Hz), 7.16 (1H, d, J=9.83 Hz);

Mass (APCI): 287 $(M+H)^+$;

Anal. Calcd for $C_8H_9F_3N_2O_4S$: C, 33.57; H, 3.17; N, 9.79.
Found: C, 33.80; H, 2.96; N, 9.79.

Preparation 3

In the presence of bis(triphenylphosphine)palladium(II) dichloride (0.368 g) and copper(I) iodide (0.100 g), a solution of triethylamine (8.80 mL) in dioxane (10 mL) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (15.00 g), 1-ethynylcyclohexene (6.68 g) in dioxane (50 mL) at 75-80°C for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, a mixture of water and chloroform was added to the mixture. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 9:1 v/v) to give 6-[1-(cyclohexen-1-yl)-2-ethynyl]-2-isopropyl-3(2H)-pyridazinone as a solid (12.16 g).

mp: 57-58.5°C (hexane);

IR (KBr): 2195, 1664, 1583 cm^{-1};

^1H NMR (DMSO-d_6, δ): 1.26 (6H, d, J=6.63 Hz), 1.5-1.65 (4H, m), 2.1-2.2 (4H, m), 5.13 (1H, 7-plet, J=6.63 Hz), 6.32 (1H, br. s), 6.90 (1H, d, J=9.56 Hz), 7.43 (1H, d, J=9.56 Hz) ;

Mass (APCI): 243 $(M+H)^+$, 201;

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56.
Found: C, 74.26; H, 7.53; N, 11.51.

The compounds of following Preparations 4 to 14 were prepared in a similar manner to Preparation 3.

Preparation 4

6-[2-(1-Hydroxycyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone

mp: 110-112°C (acetone-hexane);

IR (KBr): 2219, 1647, 1579 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 1.45-1.85 (8H, m), 1.93-2.1 (2H, m), 2.29 (1H, s), 5.30 (1H, 7-plet,

J=6.65 Hz), 6.83 (1H, d, J=9.50 Hz), 7.16 (1H, d, J=9.50 Hz);
Mass (APCI): 261 $(M+H)^+$, 243;
Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76.
Found: C, 69.12; H, 7.83; N, 10.76.

Preparation 5

2-Isopropyl-6-[3-(methoxymethoxy)-1-propynyl]-3(2H)-pyridazinone
IR (Neat): 3512, 1666, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.36 (6H, d, J=6.65 Hz), 3.42 (3H, s), 4.44 (2H, s), 4.76 (2H, s), 5.30 (1H, 7-plet, J=6.64 Hz), 6.84 (1H, d, J=9.54 Hz), 7.20 (1H, d, J=9.55 Hz);
Mass (APCI): 237 $(M+H)^+$, 195, 133.

Preparation 6

2-Isopropyl-6-[3-(methoxymethoxy)-1-butynyl]-3(2H)-pyridazinone
IR (Neat): 3532, 1656, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.36 (6H, d, J=6.66 Hz), 1.56 (3H, d, J=6.72 Hz), 3.42 (3H, s), 4.66 (1H, d, J=6.88 Hz), 4.67 (1H, q, J=6.73 Hz), 5.33 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.51 Hz), 7.19 (1H, d, J=9.50 Hz);
Mass (APCI): 251 $(M+H)^+$, 209.

Preparation 7

6-(3-Hydroxy-1-propynyl)-2-isopropyl-3(2H)-pyridazinone
mp: 132.5-134°C (acetone-hexane)
IR (KBr): 3382, 2231, 1647, 1579 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.26 (6H, d, J=6.63 Hz), 4.32 (2H, d, J=5.99 Hz), 5.17 (1H, 7-plet, J=6.62 Hz), 5.46 (1H, t, J=5.99 Hz), 6.92 (1H, d, J=9.57 Hz), 7.43 (1H, d, J=9.57 Hz);
Mass (APCI): 193 $(M+H)^+$, 163, 151;
Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57.
Found: C, 62.66; H, 6.33; N, 14.59.

Preparation 8

6-(3-Hydroxy-1-butynyl)-2-isopropyl-3(2H)-

pyridazinone
mp: 81-82°C (hexane);
IR (KBr): 3457, 1655, 1581 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.26 (6H, d, J=6.63 Hz), 1.38 (3H, d, J=6.62 Hz), 4.60 (1H, m), 5.13 (1H, 7-plet, J=6.62 Hz), 5.61 (1H, d, J=5.47 Hz), 6.91 (1H, d, J=9.57 Hz), 7.41 (1H, d, J=9.57 Hz);
Mass (APCI): 207 $(M+H)^+$, 165, 121;
Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58.
Found: C, 64.02; H, 6.85; N, 13.41.

Preparation 9

6-(3-Hydroxy-3-methyl-1-butynyl)-2-isopropyl-3(2H)-pyridazinone
mp: 109-110.5°C (acetone-hexane);
IR (KBr): 3326, 2233, 1647, 1577 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 1.63 (6H, s), 2.38 (1H, s), 5.30 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.52 Hz), 7.15 (1H, d, J=9.52 Hz);
Mass (APCI): 221 $(M+H)^+$, 179, 121;
Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72.
Found: C, 65.54; H, 7.52; N, 12.76.

Preparation 10

6-(3,3-Diethoxy-1-propynyl)-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 1673, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.28 (6H, t, J=7.07 Hz), 1.36 (6H, d, J=6.64 Hz), 3.58-3.89 (4H, m), 5.33 (1H, 7-plet, J=6.64 Hz), 5.48 (1H, s), 6.83 (1H, d, J=9.55 Hz), 7.22 (1H, d, J=9.55 Hz);
Mass (APCI): 265 $(M+H)^+$, 219, 176.

Preparation 11

6-[2-(1-Hydroxycyclopentyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone
mp: 106-108°C (acetone-hexane);
IR (KBr): 3326, 2233, 1645, 1579 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 1.66-2.18 (9H,

m), 5.30 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.55 Hz), 7.16 (1H, d, J=9.55 Hz);
Mass (APCI): 247 $(M+H)^+$, 229, 207, 126, 121;
Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37.
Found: C, 68.26; H, 7.41; N, 11.35.

Preparation 12

6-[2-(1-Hydroxycyclobutyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone
mp: 109-109.5°C (chloroform-hexane);
IR (KBr): 3336, 1648, 1579 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.64 Hz), 1.85-1.98 (2H, m), 2.2-2.45 (2H, m), 2.49-2.64 (2H, m), 2.65 (1H, s), 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.54 Hz), 7.17 (1H, d, J=9.54 Hz);
Mass (APCI): 233 $(M+H)^+$, 191, 163, 121;
Anal. Calcd for $C_{13}H_{16}N_2O_2 \cdot 0.1H_2O$: C, 66.70; H, 6.98; N, 11.97.
Found: C, 66.86; H, 7.05; N, 11.95.

Preparation 13

6-(3-Hydroxy-3-methyl-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone
mp: 92-93°C (acetone-hexane);
IR (KBr): 3390, 1660, 1581 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.10 (3H, t, J=7.43 Hz), 1.36 (6H, d, J=6.65 Hz), 1.58 (3H, s), 1.81 (2H, q, J=7.43 Hz), 2.25 (1H, s), 5.29 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.53 Hz), 7.16 (1H, d, J=9.53 Hz);
Mass (APCI): 235 $(M+H)^+$, 193, 163, 121;
Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96.
Found C, 66.55; H, 7.77; N, 11.94.

Preparation 14

6-(3-Ethyl-3-hydroxy-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone
mp: 88-89.5°C (isopropyl ether-hexane);
IR (KBr): 3363, 2219, 1648, 1579 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.10 (6H, t, J=7.41 Hz), 1.36 (6H, d,

J=6.65 Hz), 1.7-2.05 (4H, m), 2.09 (1H, s), 5.29 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.52 Hz), 7.16 (1H, d, J=9.52 Hz);
Mass (APCI): 249 $(M+H)^+$, 231, 207, 189, 163, 121;
Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28.
Found: C, 67.88; H, 8.37; N, 11.38.

Example 1

A mixture of 6-[2-(1-cyclohexen-1-yl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (123.8 mg), 1-aminopyridinium iodide (112.7 mg) and potassium carbonate (208.2 mg) in dimethylformamide (0.5 mL) was stirred at 100-105°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (112.7 mg) was added and stirred at 100-105°C for 1 hour. Furthermore 1-aminopyridinium iodide (112.7 mg) was added and stirred at the same temperature for 4.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 8:2 v/v) to give 6-[2-(1-cyclohexen-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (67.1 mg).
mp: 118-119°C (acetone-hexane);
IR (KBr): 1654, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 1.65-1.95 (2H, m), 2.17-2.3 (2H, m), 2.4-2.55 (2H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 6.8-6.88 (1H, m), 6.91 (1H, d, J=9.62 Hz), 7.2-7.29 (1H, m), 7.48 (1H, d, J=9.62 Hz), 7.91-7.97 (1H, m), 8.44 (1H, d, J=6.95 Hz);
Mass (APCI): 335 $(M+H)^+$.

The following compounds of Preparations 15 to 17 were prepared in a similar manner to Example 1.

Preparation 15

6-[2-(1-Hydroxycyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 159.5-161°C (acetone-hexane);

IR (KBr): 3282, 1649, 1579 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.25-2.18 (10H, m), 1.45 (6H, d, J=6.72 Hz), 4.92 (1H, s), 5.48 (1H, 7-plet, J=6.72 Hz), 6.80-6.89 (1H, m), 7.05 (1H, d, J=9.59 Hz), 7.55 (1H, d, J=10.20 Hz), 7.59 (1H, d, J=9.60 Hz), 8.47 (1H, d, J=6.97 Hz);
Mass (APCI): 353 $(M+H)^+$, 335;
Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90.
Found: C, 67.98; H, 6.98; N, 15.68.

Preparation 16

6-[2-(Hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 153.5-154.5°C (chloroform-isopropyl ether);
IR (KBr): 3222, 1670, 1600 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.39 (6H, d, J=6.62 Hz), 4.79 (2H, s), 5.27 (1H, 7-plet, J=6.62 Hz), 6.01 (1H, br. s), 7.00-7.07 (2H, m), 7.40-7.49 (1H, m), 7.98-8.09 (2H, m), 8.74 (1H, d, J=6.94 Hz);
Mass (APCI): 285 $(M+H)^+$;
Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71.
Found: C, 63.10; H, 5.54; N, 19.58.

Preparation 17

6-[2-(1-Hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 162-163°C (methanol);
IR (KBr): 3369, 1649, 1579 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.37 (6H, d, J=6.61 Hz), 1.56 (3H, d, J=6.48 Hz), 5.1-5.2 (1H, m), 5.26 (1H, 7-plet, J=6.61 Hz), 5.46 (1H, br. s), 6.95-7.03 (2H, m), 7.36-7.45 (1H, m), 7.94 (1H, d, J=9.00 Hz), 8.02 (1H, d, J=9.66 Hz), 8.74 (1H, d, J=6.84 Hz);
Mass (APCI): 299 $(M+H)^+$, 281;
Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78.
Found C, 64.44; H, 6.17; N, 18.80.

Preparation 18

A mixture of 6-(3-hydroxy-3-methyl-1-butynyl)-2-isopropyl-3(2H)-pyridazinone (1.11 g), 1-aminopyridinium

iodide (0.56 g) and potassium carbonate (1.75 g) in dimethylformamide (5 mL) was stirred at 100-105°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (0.56 g) was added and stirred at 100-105°C for 0.5 hour. This procedure was repeated twice. The mixture was stirred at the same temperature for 4.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 5:5 v/v) to give 6-[2-(1-hydroxy-1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.7 g).
mp: 132.5-134°C (acetone-hexane);
IR (KBr): 3330-3275, 1653, 1583 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45 (6H, d, J=6.73 Hz), 1.69 (6H, s), 5.29 (1H, s), 5.49 (1H, 7-plet, J=6.73 Hz), 6.81-6.90 (1H, m), 7.07 (1H, d, J=9.62 Hz), 7.20-7.31 (1H, m), 7.52-7.60 (1H, m), 7.61 (1H, d, J=9.64 Hz), 8.47 (1H, d, J=6.98 Hz);
Mass (APCI): 313 $(M+H)^+$, 295;
Anal. Calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94.
Found: C, 65.52; H, 6.62; N, 17.92.

The following compounds of Preparations 19 to 22 were prepared in a similar manner to Preparation 18.

Preparation 19

2-Isopropyl-6-{2-[1-(methoxymethoxy)ethyl]-pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone
mp: 93-94°C (isopropyl ether);
IR (KBr): 1664, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.44 (3H, d, J=5.16 Hz), 1.47 (3H, d, J=5.18 Hz), 1.67 (6H, d, J=6.68 Hz), 3.35 (3H, s), 4.66 (1H, d, J=6.80 Hz), 4.69 (1H, d, J=6.80 Hz), 5.35 (1H, q, J=6.67 Hz), 5.45 (1H, 7-plet, J=6.67 Hz), 6.82-6.91 (1H, m), 7.00 (1H, d, J=9.60 Hz), 7.20-7.31 (1H, m), 7.74-7.84 (2H, m), 8.50 (1H, d, J=6.98 Hz);
Mass (APCI): 343 $(M+H)^+$, 281;

Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36.
Found: C, 63.16; H, 6.59; N, 16.37.

Preparation 20

2-Isopropyl-6-{2-[1-(methoxymethoxy)methyl]-pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone
mp: 93-94°C (isopropyl ether);
IR (KBr): 1664, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.44 (3H, d, J=5.16 Hz), 1.47 (3H, d, J=5.18 Hz), 1.67 (6H, d, J=6.68 Hz), 3.35 (3H, s), 4.66 (1H, d, J=6.80 Hz), 4.69 (1H, d, J=6.80 Hz), 5.35 (1H, q, J=6.67 Hz), 5.45 (1H, 7-plet, J=6.67 Hz), 6.82-6.91 (1H, m), 7.00 (1H, d, J=9.60 Hz), 7.20-7.31 (1H, m), 7.74-7.84 (2H, m), 8.50 (1H, d, J=6.98 Hz);
Mass (APCI): 343 $(M+H)^+$, 281;
Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36.
Found: C, 63.16; H, 6.59; N, 16.37.

Preparation 21

6-[2-(Diethoxymethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 92-93°C (acetone-hexane);
IR (KBr): 1655, 1585 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.21 (6H, t, J=7.05 Hz), 1.47 (6H, d, J=6.64 Hz), 3.52-3.86 (4H, m), 5.46 (1H, 7-plet, J=6.63 Hz), 5.92 (1H, s), 6.81-6.92 (1H, m), 6.94 (1H, d, J=9.66 Hz), 7.23-7.33 (1H, m), 7.98-8.15 (2H, m), 8.47 (1H, d, J=6.99 Hz);
Mass (APCI): 357 $(M+H)^+$, 329, 311;
Anal. Calcd for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72.
Found: C, 63.82; H, 6.82; N, 15.57.

Preparation 22

6-[2-(1-Hydroxycyclopentyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 118-120°C (hexane);
IR (KBr): 3371, 1658, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45 (6H, d, J=6.74 Hz), 1.7-2.28 (8H, m), 4.88 (1H, s), 5.49 (1H, 7-plet, J=6.73 Hz), 6.80-6.89 (1H, m), 7.06 (1H, d, J=9.60 Hz), 7.21-7.30 (1H, m), 7.57 (1H, d, J=9.04 Hz), 7.63 (1H, d, J=9.62 Hz), 8.47 (1H, d, J=6.98 Hz);
Mass (APCI): 339 $(M+H)^+$, 321, 279;
Anal. Calcd for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56.
Found: C, 67.39; H, 6.56; N, 16.53.

Preparation 23

A mixture of 6-(3-hydroxy-3-methyl-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone (235 mg), 1-aminopyridinium iodide (112 mg) and potassium carbonate (553 mg) in dimethylformamide (1 mL) was stirred at 100-105°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (0.56 g) was added and stirred at 100-105°C for 0.5 hour. This procedure was repeated twice. The mixture was stirred at the same temperature for 2.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 3:7 v/v) to give 6-[2-(1-hydroxy-1-methylpropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a syrup (261 mg).
IR (Neat): 3460-3360, 1656, 1585, 1529 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.87 (3H, t, J=7.44 Hz), 1.43 (3H, d, J=6.12 Hz), 1.46 (3H, d, J=6.42 Hz), 1.69 (3H, s), 1.80-2.01 (2H, m), 4.95 (1H, s), 5.47 (1H, 7-plet, J=6.72 Hz), 6.80-6.89 (1H, m), 7.05 (1H, d, J=9.62 Hz), 7.20-7.29 (1H, m), 7.49-7.59 (2H, m), 8.44-8.49 (1H, m);
Mass (ESI): 675 $(2M+Na)^+$, 349 $(M+Na)^+$, 327 $(M+H)^+$, 309.

Preparation 24

6-[2-(1-Ethyl-1-hydroxypropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (236 mg) was prepared as a solid, from 6-(3-ethyl-3-hydroxy-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone (250 mg) and 1-aminopyridinium iodide (448 mg) in a similar manner to that of Preparation 23.

mp: 124.5-125.5°C (acetone-hexane);
IR (KBr): 3361, 1640, 1582 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.86 (3H, t, J=7.40 Hz), 1.43 (6H, d, J=6.70 Hz), 1.85-2.12 (4H, m), 4.39 (1H, s), 5.45 (1H, 7-plet, J=6.69 Hz), 6.79-6.88 (1H, m), 7.02 (1H, d, J=9.56 Hz), 7.16-7.27 (1H, m), 7.43-7.55 (2H, m), 8.43-8.48 (1H, m);
Mass (ESI): 703 $(2M+Na)^+$, 363 $(M+Na)^+$, 341 $(M+H)^+$;
Anal. Calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46.
Found: C, 67.28; H, 7.29; N, 16.38.

Preparation 25

A mixture of 2-isopropyl-6-[3-(methoxymethoxy)-1-propynyl]-3(2H)-pyridazinone (23.63 g), 1-aminopyridinium iodide (11.11 g) and potassium carbonate (55.29 g) in dimethylformamide (100 mL) was stirred at 95-100°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (1.36 g) was added and stirred at 95-100°C for 0.5 hour. This procedure was repeated twice. The mixture was stirred at the same temperature for 2.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel. Elution with a mixture of hexane and ethyl acetate (1:1 v/v) afforded 2-isopropyl-6-{3-[(methoxymethoxy)methyl]pyrazolo[1,5-a]pyridin-2-yl}-3(2H)-pyridazinone as a solid (0.06 g). Elution with ethyl acetate afforded 2-isopropyl-6-{2-[(methoxymethoxy)methyl]-pyrazolo[1,5-a]pyridin-3-yl}-4,5-dihydro-3(2H)-pyridazinone as a solid (0.36 g) and then, 2-isopropyl-6-{2-[(methoxymethoxy)methyl]pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone which was recrystallized from isopropyl ether to give a first crop (24.40 g). Concentration of the mother liquor afforded a second crop (1.88 g).

(1) 2-Isopropyl-6-{2-[(methoxymethoxy)methyl]-pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone
mp: 86-87.5°C (isopropyl ether);

IR (KBr): 1666, 1590 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 3.44 (3H, s), 4.79 (2H, s), 4.95 (2H, s), 5.45 (1H, 7-plet, J=6.63 Hz), 6.85-6.93 (1H, m), 7.01 (1H, d, J=9.62 Hz), 7.25-7.34 (1H, m), 7.78 (1H, d, J=9.64 Hz), 7.99 (1H, d, J=9.01 Hz), 8.50 (1H, d, J=7.00 Hz);
Mass (APCI): 329 $(M+H)^+$, 267;
Anal. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06.
Found: C, 62.18; H, 6.24; N, 17.09.

(2) 2-Isopropyl-6-{2-[(methoxymethoxy)methyl]-pyrazolo[1,5-a]pyridin-3-yl}-4,5-dihydro-3(2H)-pyridazinone
mp: 75.5-77°C (isopropyl ether);
IR (KBr): 1653, 1522 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.31 (6H, d, J=6.64 Hz), 2.60 (2H, t, J=8.02 Hz), 3.07 (2H, t, J=8.02 Hz), 3.44 (3H, s), 4.78 (2H, s), 4.97 (2H, s), 5.09 (1H, 7-plet, J=6.63 Hz), 6.85-6.92 (1H, m), 7.25-7.34 (1H, m), 8.05 (1H, d, J=8.98 Hz), 8.48 (1H, d, J=6.92 Hz);
Mass (APCI): 331 $(M+H)^+$, 299, 269;
Anal. Calcd for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96.
Found: C, 62.06; H, 6.74; N, 16.77.

(3) 2-Isopropyl-6-{3-[(methoxymethoxy)methyl]-pyrazolo[1,5-a]pyridin-2-yl}-3(2H)-pyridazinone
mp: 104-106°C (isopropyl ether);
IR (KBr): 1662, 1597 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.63 Hz), 3.42 (3H, s), 4.73 (2H, s), 5.18 (2H, s), 5.43 (1H, 7-plet, J=6.63 Hz), 6.79-6.87 (1H, m), 7.00 (1H, d, J=9.63 Hz), 7.13-7.22 (1H, m), 7.73 (1H, d, J=8.96 Hz), 8.06 (1H, d, J=9.63 Hz), 8.41 (1H, d, J=6.98 Hz);
Mass (ESI): 679 $(2M+Na)^+$, 351 $(M+Na)^+$, 329 $(M+H)^+$, 261;
Anal. Calcd for $C_{17}H_{20}N_4O_3 \cdot 0.2H_2O$: C, 61.51; H, 6.19; N, 16.88.
Found C: 61.40; H: 6.10; N: 16.77.

Preparation 26

A mixture of 2-isopropyl-6-[3-(methoxymethoxy)-1-

butynyl]-3(2H)-pyridazinone (25.03 g), 1-aminopyridinium iodide (11.11 g) and potassium carbonate (55.29 g) in dimethylformamide (100 mL) was stirred at 95-100°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (25.00 g) was added and stirred at 95-100°C for 0.5 hour. This procedure was repeated twice. The mixture was stirred at the same temperature for 2.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel. Elution with a mixture of hexane and ethyl acetate (2:1 v/v) afforded 2-isopropyl-6-{3-[1-(methoxymethoxy)ethyl]-pyrazolo[1,5-a]pyridin-2-yl}-3(2H)-pyridazinone as a solid (0.02 g). Elution with a mixture of hexane and ethyl acetate (1:1 v/v) afforded 2-isopropyl-6-{2-[1-(methoxymethoxy)ethyl]pyrazolo[1,5-a]pyridin-3-yl}-4,5-dihydro-3(2H)-pyridazinone as a solid (0.21 g) and, next, 2-isopropyl-6-{2-[1-(methoxymethoxy)ethyl]pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone which was recrystallized from isopropyl ether to give a first crop (23.74 g). Concentration of the mother liquor afforded a second crop (2.11 g).

(1) 2-Isopropyl-6-{2-[1-(methoxymethoxy)ethyl]-pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone
mp: 93-94°C (isopropyl ether);
IR (KBr): 1664, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.44 (3H, d, J=5.16 Hz), 1.47 (3H, d, J=5.18 Hz), 1.67 (6H, d, J=6.68 Hz), 3.35 (3H, s), 4.66 (1H, d, J=6.80 Hz), 4.69 (1H, d, J=6.80 Hz), 5.35 (1H, q, J=6.67 Hz), 5.45 (1H, 7-plet, J=6.67 Hz), 6.82-6.91 (1H, m), 7.00 (1H, d, J=9.60 Hz), 7.20-7.31 (1H, m), 7.74-7.84 (2H, m), 8.50 (1H, d, J=6.98 Hz);
Mass (APCI): 343 $(M+H)^+$, 281;
Anal. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36.
Found: C, 63.16; H, 6.59; N, 16.37.

(2) 2-Isopropyl-6-{2-[1-(methoxymethoxy)ethyl]-pyrazolo[1,5-a]pyridin-3-yl}-4,5-dihydro-3(2H)-pyridazinone
mp: 116-118°C (isopropyl ether);
IR (KBr): 1660, 1529 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.28 (3H, d, J=6.39 Hz), 1.31 (3H, d, J=6.33 Hz), 1.68 (3H, d, J=6.61 Hz), 2.55-2.64 (2H, m), 2.97-3.09 (2H, m), 3.36 (3H, s), 4.66 (1H, d, J=6.77 Hz), 4.70 (1H, d, J=6.77 Hz), 5.00-5.18 (1H, m), 5.45 (1H, q, J=6.61 Hz), 6.80-6.89 (1H, m), 7.20-7.30 (1H, m), 7.74-7.83 (1H, m), 8.47-8.51 (1H, m);
Mass (ESI): 771 $(2M+Na)^+$, 367 $(M+Na)^+$, 345 $(M+H)^+$, 283;
Anal. Calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27.
Found: C, 62.99; H, 7.07; N, 16.31.

(3) 2-Isopropyl-6-{3-[1-(methoxymethoxy)ethyl]-pyrazolo[1,5-a]pyridin-2-yl}-3(2H)-pyridazinone
mp: 139.5-141.5°C (isopropyl ether-hexane);
IR (KBr): 1664, 1599 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.43 (3H, d, J=6.67 Hz), 1.47 (3H, d, J=6.70 Hz), 1.65 (3H, d, J=6.53 Hz), 3.36 (3H, s), 4.57 (2H, s), 5.37-5.52 (1H, m), 5.88 (1H, q, J=6.52 Hz), 6.77-6.85 (1H, m), 7.00 (1H, d, J=9.65 Hz), 7.07-7.16 (1H, m), 7.88 (1H, d, J=9.02 Hz), 8.05 (1H, d, J=9.64 Hz), 8.40 (1H, d, J=7.03 Hz);
Mass (APCI): 343 $(M+H)^+$, 313, 281;
Anal. Calcd for $C_{18}H_{22}N_4O_3 \cdot 0.2H_2O$: C, 62.48; H, 6.53; N, 16.19.
Found: C, 62.72; H, 6.48; N, 16.22.

Preparation 27

A mixture of 6-(3-hydroxy-1-butynyl)-2-isopropyl-3(2H)-pyridazinone (69.01 g), 1-aminopyridinium iodide (25.00 g) and potassium carbonate (185.0 g) in dimethylformamide (335 mL) was stirred at 95-100°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (25.00 g) was added and stirred at 95-100°C for 0.5 hour. This procedure was repeated for four times. The mixture was stirred at the same temperature for 3.5 hours. After

cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 3:7 v/v and ethyl acetate only). First was eluted 6-[2-(1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-4,5-dihydro-3(2H)-pyridazinone (7.93 g). Next was eluted 6-[2-(1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone which was recrystallized from methanol to give a first crop (44.53 g). Concentration of the mother liquor afforded a second crop (12.87 g).

(1) 6-[2-(1-Hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 162-163°C (methanol);
IR (KBr): 3369, 1649, 1579 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.37 (6H, d, J=6.61 Hz), 1.56 (3H, d, J=6.48 Hz), 5.1-5.2 (1H, m), 5.26 (1H, 7-plet, J=6.61 Hz), 5.46 (1H, br. s), 6.95-7.03 (2H, m), 7.36-7.45 (1H, m), 7.94 (1H, d, J=9.00 Hz), 8.02 (1H, d, J=9.66 Hz), 8.74 (1H, d, J=6.84 Hz);
Mass (APCI): 299 $(M+H)^+$, 281;
Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78.
Found: C, 64.44; H, 6.17; N, 18.80.

(2) 6-[2-(1-Hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-4,5-dihydro-3(2H)-pyridazinone
mp: 145-147°C (methanol);
IR (KBr): 3363, 1653, 1529 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.21 (6H, d, J=6.64 Hz), 1.56 (3H, d, J=6.44 Hz), 2.44-2.53 (2H, m), 2.9-3.3 (2H, m), 4.94 (1H, 7-plet, J=6.64 Hz), 5.10-5.24 (1H, m), 5.35 (1H, d, J=5.66 Hz), 6.95-7.02 (1H, m), 7.35-7.44 (1H, m), 7.94 (1H, d, J=9.01 Hz), 8.71 (1H, d, J=6.89 Hz);
Mass (APCI): 301 $(M+H)^+$, 283;
Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65.
Found: C, 64.02; H, 6.73; N, 18.60.

Preparation 28

A solution of 2-isopropyl-6-(2-[(methoxymethoxy)-methyl]pyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (2.03 g) in a mixture of 1N hydrochloric acid (4 mL) and dioxane (36 mL) was heated under reflux for 12 hours. The mixture was cooled, neutralized with aqueous sodium hydrogencarbonate solution, and extracted with chloroform. The chloroform solution was dried over magnesium sulfate, concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol-chloroform 2:98 v/v) to give 6-[2-(hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.46 g).
mp: 153.5-154.5°C (chloroform-isopropyl ether);
IR (KBr): 3222, 1670, 1600 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.39 (6H, d, J=6.62 Hz), 4.79 (2H, s), 5.27 (1H, 7-plet, J=6.62 Hz), 6.01 (1H, br. s), 7.00-7.07 (2H, m), 7.40-7.49 (1H, m), 7.98-8.09 (2H, m), 8.74 (1H, d, J=6.94 Hz);
Mass (APCI): 285 $(M+H)^+$;
Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71.
Found: C, 63.10; H, 5.54; N, 19.58.

The following compound of Preparation 29 was prepared in a similar manner to Preparation 28.

Preparation 29

6-[2-(1-Hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 132.5-134°C (acetone-hexane);
IR (KBr): 3330-3275, 1653, 1583 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45 (6H, d, J=6.73 Hz), 1.69 (6H, s), 5.29 (1H, s), 5.49 (1H, 7-plet, J=6.73 Hz), 6.81-6.90 (1H, m), 7.07 (1H, d, J=9.62 Hz), 7.20-7.31 (1H, m), 7.52-7.60 (1H, m), 7.61 (1H, d, J=9.64 Hz), 8.47 (1H, d, J=6.98 Hz);
Mass (APCI): 313 $(M+H)^+$, 295;
Anal. Calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94.
Found: C, 65.52; H, 6.62; N, 17.92.

Preparation 30

A solution of 6-[2-(diethoxymethyl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (15.01 g) in a mixture of 1N hydrochloric acid (30 mL) and tetrahydrofuran (270 mL) was heated under reflux for 6 hours. The mixture was cooled, neutralized by aqueous sodium hydrogencarbonate solution, and extracted with chloroform. The chloroform solution was dried over magnesium sulfate, concentrated under reduced pressure, and the resulting residue was crystallized from a mixture of acetone and hexane to give 3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)pyrazolo[1,5-a]pyridine-2-carbaldehyde (9.72 g).

mp: 154-155°C (acetone-hexane);

IR (KBr): 1700, 1664, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.64 Hz), 5.46 (1H, 7-plet, J=6.64 Hz), 7.00 (1H, d, J=9.66 Hz), 7.04-7.12 (1H, m), 7.32-7.41 (1H, m), 7.88 (1H, d, J=9.66 Hz), 8.09 (1H, d, J=9.08 Hz), 8.55 (1H, d, J=7.06 Hz), 10.31 (1H, s);

Mass (ESI): 305 $(M+Na)^+$, 283 $(M+H)^+$;

Anal. Calcd for $C_{15}H_{14}N_4O_2 \cdot 0.1H_2O$: C, 63.41; H, 5.04; N, 19.72.

Found: C, 63.38; H, 5.03; N, 19.64.

Preparation 31

A suspension of 6-[2-(hydroxymethyl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (4.07 g) and manganese(IV) oxide (40.0 g) in chloroform (100 mL) was stirred at ambient temperature for 18 hours. Insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was triturated with isopropyl ether and collected by filtration to give 3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)pyrazolo[1,5-a]pyridine-2-carbaldehyde as a solid (3.06 g).

mp: 154-155°C (acetone-hexane);

IR (KBr): 1700, 1664, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.64 Hz), 5.46 (1H, 7-plet, J=6.64 Hz), 7.00 (1H, d, J=9.66 Hz), 7.04-7.12 (1H, m),

7.32-7.41 (1H, m), 7.88 (1H, d, J=9.66 Hz), 8.09 (1H, d, J=9.08 Hz), 8.55 (1H, d, J=7.06 Hz), 10.31 (1H, s);

Mass (ESI): 305 $(M+Na)^+$, 283 $(M+H)^+$;

Anal. Calcd for $C_{15}H_{14}N_4O_2 \cdot 0.1H_2O$: C, 63.41; H, 5.04; N, 19.72.

Found: C, 63.38; H, 5.03; N, 19.64.

Example 2

In the presence of Nafion® NR50 (125 mg), a solution of 6-[2-(1-hydroxycyclohexyl)pyrazolo-[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (100 mg) in glacial acetic acid (2 mL) was refluxed for 20 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 5:5 v/v) to give 6-[2-(1-cyclohexen-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (68 mg).

mp: 118-119°C (acetone-hexane);

IR (KBr): 1654, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 1.65-1.95 (2H, m), 2.17-2.3 (2H, m), 2.4-2.55 (2H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 6.8-6.88 (1H, m), 6.91 (1H, d, J=9.62 Hz), 7.2-7.29 (1H, m), 7.48 (1H, d, J=9.62 Hz), 7.91-7.97 (1H, m), 8.44 (1H, d, J=6.95 Hz);

Mass (APCI): 335 $(M+H)^+$.

Example 3

In the presence of Nafion® NR50 (100 mg), a solution of 6-[2-(1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (109.4 mg) in xylene (1 mL) was refluxed for 24 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (ethyl acetate only) to give 2-isopropyl-6-(2-vinylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone as a syrup (45.7 mg). The syrup was triturated with hexane to give a solid.

mp: 129-131°C (hexane);
IR (KBr): 1664, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 5.44 (1H, 7-plet, J=6.64 Hz), 5.57 (1H, dd, J=1.68, 11.10 Hz), 6.20 (1H, dd, J=1.66, 17.53 Hz), 6.83-6.92 (1H, m), 6.98 (1H, dd, J=11.10, 17.52 Hz), 6.99 (1H, d, J=9.58 Hz), 7.20-7.48 (1H, m), 7.50 (1H, d, J=9.58 Hz), 7.78-7.84 (1H, m), 8.45-8.50 (1H, m);
Mass (APCI): 281 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{16}N_4O \cdot 0.25H_2O$: C, 67.47; H, 5.84; N, 19.67.
Found: C, 67.70; H, 5.79; N, 19.45.

Example 4

In the presence of Nafion® NR50 (100 mg), a solution of 6-[2-(1-hydroxy-1-methylethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (104.6 mg) in xylene (1 mL) was refluxed for 24 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (ethyl acetate only) to give 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-isopropyl-3(2H)-pyridazinone as a syrup (86.8 mg). The syrup was triturated with hexane to give a solid.
mp: 89-90°C (hexane);
IR (KBr): 1679, 1594 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 2.24 (3H, s), 5.27 (1H, br. s), 5.3-5.5 (2H, m), 6.8-6.9 (1H, m), 6.91 (1H, d, J=9.59 Hz), 7.26 (1H, d, J=7.87 Hz), 7.50 (1H, d, J=9.60 Hz), 7.90 (1H, d, J=8.95 Hz), 8.45 (1H, d, J=6.97 Hz);
Mass (APCI): 295 $(M+H)^+$;
Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03.
Found: C, 69.43; H, 6.19; N, 19.00.

Example 5

In the presence of Nafion® NR50 (50 mg), a solution of 6-[2-(1-hydroxycyclopentyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (119.4 mg) in glacial acetic

acid (1 mL) was refluxed for 14 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 5:5 v/v) to give 6-[2-(1-cyclopenten-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (94.3 mg).
mp: 126-127.5°C (hexane);
IR (KBr): 1656, 1587 cm^{-1};
Mass (APCI): 321 $(M+H)^+$;
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 1.95-2.15 (2H, m), 2.5-2.65 (2H, m), 2.75-2.90 (2H, m), 5.44 (1H, 7-plet, J=6.63 Hz), 6.10 (1H, s), 6.75-6.9 (1H, m), 6.93 (1H, d, J=9.58 Hz), 7.15-7.3 (1H, m), 7.46 (1H, d, J=9.58 Hz), 7.80 (1H, d, J=8.93 Hz), 8.45 (1H, d, J=6.98 Hz);
Anal. Calcd for $C_{19}H_{20}N_4O \cdot 0.5H_2O$: C, 69.28; H, 6.42; N, 17.01.
Found: C, 69.60; H, 6.26; N, 16.94.

Example 6

In the presence of methanesulfonic acid (96 mg), a solution of 6-[2-(1-hydroxy-1-methylpropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (957 mg) in toluene (9.6 mL) was refluxed for 24 hours. The mixture was poured into chilled saturated aqueous sodium hydrogencarbonate solution, extracted with ethyl acetate, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 6:4 v/v) to give two products.

(1) 2-Isopropyl-6-{2-[(1E or 1Z)-1-methyl-1-propenyl]pyrazolo-[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone (more polar compound, 421 mg)
mp: 101-102°C (hexane);
IR (KBr): 1662, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.48 (6H, d, J=6.64 Hz), 1.83 (3H, dd, J=0.95, 6.88 Hz), 2.08-2.12 (3H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 5.85-5.90 (1H, m), 6.80-6.88 (1H, m), 6.90 (1H,

d, J=9.64 Hz), 7.20-7.29 (1H, m), 7.43 (1H, d, J=9.64 Hz), 7.90-7.96 (1H, m), 8.41-8.46 (1H, m);
Mass (APCI): 309 $(M+H)^+$, 267;
Anal. Calcd for $C_{18}H_{20}N_4O \cdot 0.2H_2O$: C, 69.30; H, 6.59; N, 17.96.
Found: C, 69.36; H, 6.59; N, 17.75.

(2) 2-Isopropyl-6-[2-(1-ethylvinyl)pyrazolo[1,5-a]-pyridin-3-yl]-3(2H)-pyridazinone (less polar compound, 102 mg)
mp: 85-86.5°C (pentane);
IR (KBr): 1664, 1593 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.16 (3H, t, J=7.38 Hz), 1.47 (6H, d, J=6.64 Hz), 2.58 (2H, q, J=7.38 Hz), 5.29 (1H, s), 5.29-5.50 (2H, m), 6.85-6.93 (2H, m), 7.22-7.31 (1H, m), 7.50 (1H, d, J=9.60 Hz), 7.94 (1H, br. d, J=8.98 Hz), 8.46 (1H, d, J=6.98 Hz);
Mass (APCI): 309 $(M+H)^+$, 267;
Anal. Calcd for $C_{18}H_{20}N_4O \cdot 0.1H_2O$: C: 69.70; H: 6.56; N: 18.06.
Found C: 69.76; H: 6.57; N: 18.09.

Preparation 32

In the presence of bis(triphenylphosphine)palladium(II) dichloride (1.47 g) and copper(I) iodide (1.47 g), a solution of triethylamine (14.67 mL) in dioxane (25 mL) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (20.10 g), ethynyl(trimethyl)silane (24.81 mL) in tetrahydrofuran (300 mL) at 5-10°C for 0.5 hour. The mixture was stirred at the same temperature for 1.5 hours and at ambient temperature for 3 hours. Ethyl acetate was added to the reaction mixture. The mixture was washed with 10% aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 9:1 v/v) to give 2-isopropyl-6-[2-(trimethylsilyl)-1-ethynyl]-3(2H)-pyridazinone as a solid (16.10 g).

mp: 40-41°C (hexane);
IR (KBr): 2160, 1664, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.27 (9H, s), 1.37 (6H, d, J=6.65 Hz), 5.29 (1H, 7-plet, J=6.65 Hz), 6.81 (1H, d, J=9.50 Hz), 7.21 (1H, d, J=9.50 Hz);
Mass (ESI): 491 $(2M+Na)^+$, 257 $(M+Na)^+$, 235 $(M+H)^+$, 193;
Anal. Calcd for $C_{12}H_{16}N_2OSi$: C, 61.50; H, 7.74; N, 11.95.
Found: C, 61.25; H, 7.82; N, 12.00.

Preparation 33

In the presence of benzyltriethylammonium chloride (0.52 g), 12N aqueous sodium hydroxide solution (60 mL) was added to a solution of 2-isopropyl-6-[2-(trimethylsilyl)-1-ethynyl]-3(2H)-pyridazinone (15.75 g) in a mixture of tetrahydrofuran (45 mL) and acetonitrile (45 mL) under ice-cooling and the mixture was stirred at the same temperature for 0.5 hour. Under ice-cooling, the reaction mixture was acidified with concentrated hydrochloric acid, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 8:2 v/v) to give 6-ethynyl-2-isopropyl-3(2H)-pyridazinone as a solid (10.42 g).
mp: 103-104°C (acetone-hexane);
IR (KBr): 3193, 2107, 1655, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 3.19 (1H, s), 5.31 (1H, 7-plet, J=6.65 Hz), 6.85 (1H, d, J=9.53 Hz), 7.22 (1H, d, J=9.53 Hz);
Mass (APCI): 163 $(M+H)^+$, 121;
Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27.
Found: C, 66.92; H, 6.28; N, 17.36.

Preparation 34

Below -65°C, 1.6N butyllithium solution in hexane (4.25 mL) was added dropwise to a solution of 6-ethynyl-2-isopropyl-3(2H)-pyridazinone (1.00 g) in tetrahydrofuran (20 mL). After 0.5 hour, cyclobutanone (0.51 mL) was added at the same temperature. The mixture was stirred at the

same temperature for 0.5 hour and allowed to warm to ambient temperature over 4 hours. After addition of aqueous ammonium chloride solution, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a syrup. The syrup was purified by column chromatography on silica gel (hexane-ethyl acetate 5:5 v/v) to give 6-[2-(1-hydroxycyclobutyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone as a solid (0.26 g).

mp: 109-109.5°C (chloroform-hexane);

IR (KBr): 3336, 1648, 1579 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.64 Hz), 1.85-1.98 (2H, m), 2.2-2.45 (2H, m), 2.49-2.64 (2H, m), 2.65 (1H, s), 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.54 Hz), 7.17 (1H, d, J=9.54 Hz);

Mass (APCI): 233 $(M+H)^+$, 191, 163, 121;

Anal. Calcd for $C_{13}H_{16}N_2O_2 \cdot 0.1H_2O$: C, 66.70; H, 6.98; N, 11.97.

Found: C, 66.86; H, 7.05; N, 11.95.

The following compounds of Preparations 35 to 47 were prepared in a similar manner to Preparation 34.

Preparation 35

6-[2-(1-Hydroxycycloheptyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone

mp: 173-174.5°C (isopropyl ether);

IR (KBr): 3396, 2219, 1654, 1644, 1581 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 1.5-2.25 (13H, m), 5.29 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.53 Hz), 7.17 (1H, d, J=9.53 Hz);

Mass (APCI): 275 $(M+H)^+$, 257, 233, 163, 121;

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21.

Found: C, 70.18; H, 8.00; N, 10.19.

Preparation 36

6-[2-(1-Hydroxycyclooctyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone

mp: 121-122°C (acetone-isopropyl ether);

IR (KBr): 3334, 2219, 1648, 1579 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.36 (6H, d, J=6.65 Hz), 1.4-2.2 (15H, m), 5.29 (1H, 7-plet, J=6.65 Hz), 6.82 (1H, d, J=9.51 Hz), 7.16 (1H, d, J=9.51 Hz);

Mass (APCI): 289 $(M+H)^+$, 271, 163, 121;

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71.

Found: C, 70.80; H, 8.52; N, 9.66.

Preparation 37

The two stereoisomers (less polar isomer; 0.41 g, more polar isomer; 0.49 g) of 6-[2-(1-hydroxy-2-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone were prepared as solids from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone (1.00 g) and 2-methylcyclohexanone (0.83 mL), respectively.

(1) 6-[2-(1-Hydroxy-2-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (less polar isomer)

mp: 138-139.5°C (acetone-hexane);

IR (KBr): 3355, 2233, 1643, 1583 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.12 (3H, d, J=6.78 Hz), 1.1-1.85 (8H, m), 1.36 (6H, d, J=6.65 Hz), 1.86 (1H, s), 2.05-2.15 (1H, m), 5.29 (1H, 7-plet, J=6.65 Hz), 6.82 (1H, d, J=9.25 Hz), 7.16 (1H, d, J=9.25 Hz);

Mass (APCI): 275 $(M+H)^+$, 257, 163, 121;

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21.

Found: C, 70.31; H, 8.13; N, 10.24.

(2) 6-[2-(1-Hydroxy-2-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (more polar isomer)

mp: 122.5-123.5°C (acetone-hexane);

IR (KBr): 3392, 2219, 1652, 1581 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.12 (3H, d, J=6.36 Hz), 1.2-1.8 (8H, m), 1.37 (6H, d, J=6.65 Hz), 2.1-2.2 (1H, m), 2.25 (1H, s), 5.30 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.50 Hz), 7.18 (1H, d, J=9.50 Hz);

Mass (APCI): 275 $(M+H)^+$, 257, 233, 163, 121;

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21.

Found: C, 70.27; H, 8.13; N, 10.25.

Preparation 38

The two stereoisomers (less polar isomer; 0.07 g, more polar isomer; 0.47 g) of 6-[2-(1-hydroxy-4-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone were prepared as solids, from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone (1.00 g) and 4-methylcyclohexanone (0.84 mL), respectively.

(1) 6-[2-(1-Hydroxy-4-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (less polar isomer)
mp: 138-141°C (ethyl acetate-hexane);
IR (KBr): 3330, 2219, 1646, 1577 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.94 (3H, d, J=5.65 Hz), 1.3-2.1 (9H, m), 1.36 (6H, d, J=6.65 Hz), 1.96 (1H, s), 5.29 (1H, 7-plet, J=6.65 Hz), 6.82 (1H, d, J=9.53 Hz), 7.15 (1H, d, J=9.53 Hz);
Mass (APCI): 275 $(M+H)^+$, 257, 233, 163, 121;
Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21.
Found: C, 70.09; H, 8.40; N, 10.13.

(2) 6-[2-(1-Hydroxy-4-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (more polar isomer)
mp: 140-141.5°C (chloroform-isopropyl ether);
IR (KBr): 3374, 2219, 1648, 1581 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.95 (3H, d, J=5.82 Hz), 1.0-2.15 (9H, m), 1.37 (6H, d, J=6.65 Hz), 2.34 (1H, s), 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.51 Hz), 7.17 (1H, d, J=9.51 Hz);
Mass (APCI): 275 $(M+H)^+$, 257, 233, 163, 121;
Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21.
Found: C, 70.05; H, 8.12; N, 10.15.

Preparation 39

6-[2-(1-Hydroxy-4,4-dimethylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 3409, 2219, 1664, 1635, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.96 (6H, s), 1.0-2.1 (9H, m), 1.37 (6H, d, J=6.65 Hz), 5.30 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.53 Hz), 7.17 (1H, d, J=9.53 Hz);

Mass (APCI): 289 $(M+H)^+$, 271, 163, 121.

Preparation 40

6-[2-(3-Hydroxy-2-methyltetrahydrofuran-3-yl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 3409, 2219, 1658, 1583 cm^{-1};
^1H NMR ($CDCl_3$, δ): 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.54 Hz), 7.18 (1H, d, J=9.54 Hz);
Mass (APCI): 263 $(M+H)^+$, 221, 163, 121.

Preparation 41

6-[2-(4-Hydroxytetrahydro-2H-pyran-4-yl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 3413, 2219, 1666, 1650, 1583 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 1.14-1.3 (5H, m), 3.65-4.02 (4H, m), 5.30 (1H, 7-plet, J=6.65 Hz), 6.85 (1H, d, J=9.54 Hz), 7.17 (1H, d, J=9.54 Hz);
Mass (APCI): 263 $(M+H)^+$, 221, 163, 121.

Preparation 42

6-[2-(4-Hydroxytetrahydro-2H-thiopyran-4-yl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone
mp: 155-156°C (acetone-hexane);
IR (KBr): 3336, 2233, 1637, 1573 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.37 (6H, d, J=6.65 Hz), 1.95-2.15 (2H, m), 2.2-2.35 (2H, m), 2.48 (1H, s), 2.7-2.9 (4H, m), 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.54 Hz), 7.15 (1H, d, J=9.54 Hz);
Mass (APCI): 279 $(M+H)^+$, 279, 163, 121;
Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06.
Found: C, 60.57; H, 6.52; N, 10.05.

Preparation 43

6-(3-Hydroxy-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 3403, 2219, 1652, 1583 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.08 (3H, t, J=7.37 Hz), 1.36 (6H, d, J=6.65 Hz), 1.75-1.95 (2H, m), 2.16 (1H, d, J=5.61 Hz), 4.55 (1H, m), 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.53 Hz), 7.18 (1H, d, J=9.53 Hz);

Mass (APCI): 221 $(M+H)^+$, 179, 163, 121.

Preparation 44

6-(3-Hydroxy-4-methyl-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone

mp: 85.5-87°C (hexane);

IR (KBr): 3388, 2233, 1658, 1585 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.07 (3H, t, J=6.75 Hz), 1.08 (3H, t, J=6.73 Hz), 1.36 (6H, d, J=6.65 Hz), 1.9-2.15 (1H, m), 2.16 (1H, d, J=6.42 Hz), 4.39 (1H, br.t, J=5.36 Hz), 5.30 (1H, 7-plet, J=6.65 Hz), 6.84 (1H, d, J=9.53 Hz), 7.17 (1H, d, J=9.53 Hz);

Mass (APCI): 235 $(M+H)^+$, 193, 163, 121.

Preparation 45

6-(3-Hydroxy-3-methyl-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone

mp: 92-93°C (acetone-hexane);

IR (KBr): 3390, 1660, 1581 cm^{-1};

Mass (APCI): 235 $(M+H)^+$, 193, 163, 121;

^1H NMR ($CDCl_3$, δ): 1.10 (3H, t, J=7.43 Hz), 1.36 (6H, d, J=6.65 Hz), 1.58 (3H, s), 1.81 (2H, q, J=7.43 Hz), 2.25 (1H, s), 5.29 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.53 Hz), 7.16 (1H, d, J=9.53 Hz);

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96.
Found: C, 66.55; H, 7.77; N, 11.94.

Preparation 46

6-(3-Hydroxy-3,4-dimethyl-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone

mp: 73-75°C (hexane);

IR (KBr): 3399, 2233, 1650, 1583 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.07 (3H, d, J=6.61 Hz), 1.10 (3H, d, J=5.94 Hz), 1.36 (6H, d, J=6.65 Hz), 1.55 (3H, s), 1.8-2.0 (1H, m), 2.14 (1H, s), 5.29 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.52 Hz), 7.16 (1H, d, J=9.52 Hz);

Mass (APCI): 245 $(M+H)^+$, 207, 189, 163, 121.

Preparation 47

6-(3-Ethyl-3-hydroxy-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone

mp: 88-89.5°C (isopropyl ether-hexane);

IR (KBr): 3363, 2219, 1648, 1579 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.10 (6H, t, J=7.41 Hz), 1.36 (6H, d, J=6.65 Hz), 1.7-2.05 (4H, m), 2.09 (1H, s), 5.29 (1H, 7-plet, J=6.65 Hz), 6.83 (1H, d, J=9.52 Hz), 7.16 (1H, d, J=9.52 Hz);

Mass (APCI): 249 $(M+H)^+$, 231, 207, 189, 163, 121;

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28.
Found: C, 67.88; H, 8.37; N, 11.38.

Preparation 48

A mixture of 6-[2-(1-hydroxycyclobutyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (268 mg), 1-aminopyridinium iodide (128 mg), and potassium carbonate (638 mg) in dimethylformamide (1.1 mL) was stirred at 100-105°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (128 mg) was added and stirred at 100-105°C for 0.5 hour. This procedure was repeated twice. The mixture was stirred at the same temperature for 2.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 4:6 v/v) to give 6-[2-(1-hydroxycyclobutyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (173 mg).

mp: 191-192°C (methanol);

IR (KBr): 3318, 1644, 1577 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.72 Hz), 1.6-2.05 (2H, m), 2.35-2.55 (2H, m), 2.65-2.8 (2H, m), 4.80 (1H, s), 5.45 (1H, 7-plet, J=6.72 Hz), 6.8-6.9 (1H, m), 7.04 (1H, d, J=9.62 Hz), 7.2-7.35 (1H, m), 7.68 (1H, d, J=8.99 Hz), 7.70 (1H, d, J=9.62 Hz), 8.49 (1H, d, J=6.98 Hz);

Mass (APCI): 325 $(M+H)^+$, 297;

Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27.
Found: C, 66.50; H, 6.24; N, 17.17.

The following compounds of Preparations 49 to 58 were

prepared in a similar manner to Preparation 48.

Preparation 49

6-[2-(1-Hydroxycycloheptyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 185-186°C (chloroform-isopropyl ether);
IR (KBr): 3342, 1646, 1581 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45 (6H, d, J=6.72 Hz), 1.45-1.9 (8H, m), 2.0-2.15 (2H, m), 2.25-2.4 (2H, m), 5.04 (1H, s), 5.47 (1H, 7-plet, J=6.72 Hz), 6.75-6.9 (1H, m), 7.05 (1H, d, J=9.59 Hz), 7.15-7.3 (1H, m), 7.53 (1H, d, J=9.01 Hz), 7.59 (1H, d, J=9.59 Hz), 8.46 (1H, d, J=6.80 Hz);
Mass (APCI): 367 $(M+H)^+$, 349, 255;
Anal. Calcd for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29.
Found: C, 68.78; H, 7.21; N, 15.28.

Preparation 50

6-[2-(1-Hydroxycyclooctyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 142-143.5°C (acetone);
IR (KBr): 3353, 1660, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45 (6H, d, J=6.72 Hz), 1.4-2.4 (10H, m), 5.00 (1H, s), 5.47 (1H, 7-plet, J=6.72 Hz), 6.75-6.9 (1H, m), 7.05 (1H, d, J=9.59 Hz), 7.15-7.3 (1H, m), 7.53 (1H, d, J=9.02 Hz), 7.59 (1H, d, J=9.59 Hz), 8.47 (1H, d, J=7.00 Hz);
Mass (APCI): 381 $(M+H)^+$, 363.

Preparation 51

A less polar stereoisomer of 6-[2-(1-hydroxy-2-methylcyclohexyl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (267 mg) was prepared as a solid, from the less polar stereoisomer of 6-[2-(1-hydroxy-2-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (275 mg) and 1-aminopyridinium iodide (448 mg).
mp: 193.5-194.5°C (acetone);
IR (KBr): 3345, 1648, 1581 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.80 (3H, d, J=6.70 Hz), 1.35-2.3 (9H, m), 1.43 (6H, d, J=6.68 Hz), 3.64 (1H, s), 5.43 (1H, 7-plet, J=6.67 Hz), 6.75-6.9 (1H, s), 6.98 (1H, d, J=9.55 Hz), 7.15-7.3 (1H, m), 7.4-7.5 (2H, m), 8.44 (1H, d, J=6.92 Hz);
Mass (APCI): 367 $(M+H)^+$, 349;
Anal. Calcd for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29.
Found: C, 68.56; H, 7.41; N, 15.13.

Preparation 52

A more polar stereoisomer of 6-[2-(1-hydroxy-2-methylcyclohexyl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (221 mg) was prepared as a syrup from the more polar stereoisomer of 6-[2-(1-hydroxy-2-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (275 mg) and 1-aminopyridinium iodide (448 mg).
IR (Neat): 3396, 1652, 1592, 1531 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.71 (3H, d, J=7.23 Hz), 1.2-2.2 (8H, m), 1.46 (3H, d, J=6.74 Hz), 1.49 (3H, d, J=6.72 Hz), 2.25-2.45 (1H, m), 5.21 (1H, d, J=1.93 Hz), 5.48 (1H, 7-plet, J=6.74 Hz), 6.75-6.9 (1H, m), 7.06 (1H, d, J=9.59 Hz), 7.15-7.3 (1H, m), 7.5-7.65 (2H, m), 8.47 (1H, d, J=6.97 Hz);
Mass (APCI): 367 $(M+H)^+$, 349, 225.

Preparation 53

A less polar stereoisomer of 6-[2-(1-hydroxy-4-methylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (39.5 mg) was prepared as a syrup from the less polar stereoisomer of 6-[2-(1-hydroxy-4-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (34.6 mg) and 1-aminopyridinium iodide (56.0 mg).
IR (Neat): 3392, 1656, 1587, 1531 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.97 (3H, d, J=5.55 Hz), 1.2-2.2 (9H, m), 1.46 (6H, d, J=6.72 Hz), 4.80 (1H, s), 5.48 (1H, 7-plet, J=6.72 Hz), 6.8-6.9 (1H, m), 7.05 (1H, d, J=9.60 Hz), 7.2-7.35 (1H, m), 7.5-7.65 (2H, m), 8.46 (1H, d, J=6.99 Hz);
Mass (APCI): 367 $(M+H)^+$, 349, 255.

Preparation 54

A more polar stereoisomer of 6-[2-(1-hydroxy-4-methylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (343 mg) was prepared as an amorphous,

from the more polar stereoisomer of 6-[2-(1-hydroxy-4-methylcyclohexyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (275 mg) and 1-aminopyridinium iodide (448 mg).
IR (KBr): 3365, 1656, 1587, 1529 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.86 (3H, d, J=6.43 Hz), 1.1-1.85 (7H, m), 1.44 (6H, d, J=6.73 Hz), 2.35-2.45 (2H, m), 5.24 (1H, s), 5.47 (1H, 7-plet, J=6.73 Hz), 6.8-6.9 (1H, m), 7.07 (1H, d, J=9.58 Hz), 7.2-7.3 (1H, m), 7.54 (1H, d, J=9.02 Hz), 7.61 (1H, d, J=9.58 Hz), 8.49 (1H, d, J=7.00 Hz);
Mass (APCI): 367 $(M+H)^+$, 349, 255.

Preparation 55

6-[2-(1-Hydroxy-4,4-dimethylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 120-121.5°C (acetone-hexane);
IR (KBr): 3332, 1671, 1652 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.92 (3H, s), 0.99 (3H, s), 1.2-1.4 (2H, m), 1.45 (6H, d, J=6.73 Hz), 1.6-1.8 (2H, m), 1.9-2.2 (4H, m), 4.91 (1H, s), 5.48 (1H, 7-plet, J=6.73 Hz), 6.8-6.9 (1H, m), 7.06 (1H, d, J=9.60 Hz), 7.2-7.3 (1H, m), 7.51-7.58 (1H, m), 7.59 (1H, d, J=9.60 Hz), 8.48 (1H, d, J=6.99 Hz);
Mass (ESI): 783 $(2M+Na)^+$, 403 $(M+Na)^+$, 381 $(M+H)^+$, 363;
Anal. Calcd for $C_{22}H_{28}N_4O_2 \cdot 0.25H_2O$: C, 68.64; H, 7.46; N, 14.55.
Found: C, 69.01; H, 7.51; N, 14.40.

Preparation 56

2-Isopropyl-6-[2-(3-hydroxy-2-methyltetrahydrofuran-3-yl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (E,Z-mixture)
mp: 172-188°C (acetone-hexane);
IR (KBr): 3301, 1646, 1575 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.38 (3H, d, J=6.22 Hz), 1.45 (3H, d, J=6.71 Hz), 1.47 (3H, d, J=6.71 Hz), 2.3-2.45 (1H, m), 2.45-2.65 (1H, m), 3.85-4.05 (1H, m), 4.1-4.25 (1H, m), 4.49 (1H, q, J=6.22 Hz), 4.72 (1H, s), 5.46 (1H, 7-plet, J=6.71 Hz), 6.8-6.95 (1H, m), 7.06 (1H, d, J=9.59 Hz), 7.2-7.35 (1H, m), 7.57 (1H, d, J=7.69 Hz), 7.60 (1H, d, J=9.59 Hz), 8.45 (1H, d, J=6.99 Hz) (data of the major isomer);
Mass (AESI): 731 $(2M+Na)^+$, 377 $(M+Na)^+$, 355 (E,Z-mixture);
Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81.
Found: C, 64.33; H, 6.29; N, 15.70.
(E,Z-mixture)

Preparation 57

6-[2-(4-Hydroxytetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 212-214°C (hexane);
IR (KBr): 3235, 1646, 1577 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45 (6H, d, J=6.74 Hz), 1.9-2.1 (2H, m), 2.2-2.4 (2H, m), 3.75-3.9 (2H, m), 3.9-4.1 (2H, m), 5.39 (1H, s), 5.49 (1H, 7-plet, J=6.74 Hz), 6.8-6.95 (1H, m), 7.08 (1H, d, J=9.61 Hz), 7.2-7.35 (1H, m), 7.57 (1H, d, J=8.99 Hz), 7.60 (1H, d, J=9.60 Hz), 8.48 (1H, d, J=6.99 Hz);
Mass (APCI): 355 $(M+H)^+$, 337, 255;
Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81.
Found: C, 64.27; H, 6.35; N, 15.47.

Preparation 58

6-[2-(4-Hydroxytetrahydro-2H-thiopyran-4-yl)pyrazolo-[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 215-218°C (chloroform-acetone);
IR (KBr): 3245, 1646, 1577 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.74 Hz), 2.3-2.4 (4H, m), 2.45-2.6 (2H, m), 3.1-3.3 (2H, m), 5.28 (1H, s), 5.48 (1H, 7-plet, J=6.74 Hz), 6.8-6.95 (1H, m), 7.08 (1H, d, J=9.61 Hz), 7.2-7.35 (1H, m), 7.5-7.65 (2H, m), 8.47 (1H, d, J=6.98 Hz);
Mass (ESI): 763 $(2M+Na)^+$, 393 $(M+Na)^+$, 371 $(M+H)^+$, 353, 304;
Anal. Calcd for $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12.
Found: C, 61.48; H, 5.97; N, 15.08.

Preparation 59

A mixture of 6-(3-hydroxy-1-pentynyl)-2-isopropyl-3(2H)-pyridazinone (221 mg), 1-aminopyridinium iodide (112 mg) and potassium carbonate (553 mg) in dimethylformamide

(1 mL) was stirred at 100-105°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (0.56 g) was added and stirred at 100-105°C for 0.5 hour. This procedure was repeated twice. The mixture was stirred at the same temperature for 2.5 hours. After cooling, the mixture was poured into water, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 1:9 v/v) to give 6-[2-(1-hydroxypropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone as a solid (173 mg).

mp: 124.5-125.5°C (acetone-hexane);

IR (KBr): 3420-3370, 1658, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.04 (3H, t, J=7.38 Hz), 1.46 (6H, d, J=6.74 Hz), 1.93-2.09 (2H, m), 3.67 (1H, d, J=6.68 Hz), 5.4-5.55 (1H, m), 5.47 (1H, 7-plet, J=6.69 Hz), 6.82-6.91 (1H, m), 7.04 (1H, d, J=9.60 Hz), 7.23-7.32 (1H, m), 7.65 (1H, d, J=9.60 Hz), 7.68-7.73 (1H, m), 8.45-8.51 (1H, m);

Mass (ESI): 647 $(2M+Na)^+$, 335 $(M+Na)^+$, 313 $(M+H)^+$;

Anal. Calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94.
Found: C, 65.37; H, 6.68; N, 17.88.

The following compounds of Preparations 60 and 61 were prepared in a similar manner to Preparation 59.

Preparation 60

6-[2-(1-Hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 132-133.5°C (acetone-hexane);

IR (KBr): 3367, 1652, 1583, 1529 cm^{-1};

^1H NMR ($CDCl_3$, δ): 0.84 (3H, t, J=6.74 Hz), 1.09 (3H, d, J=6.60 Hz), 1.45 (3H, d, J=6.70 Hz), 1.46 (3H, d, J=6.68 Hz), 2.05-2.25 (1H, m), 3.67 (1H, d, J=8.20 Hz), 4.72 (1H, t, J=8.13 Hz), 5.47 (1H, 7-plet, J=6.69 Hz), 6.82-6.91 (1H, m), 7.04 (1H, d, J=9.58 Hz), 7.23-7.32 (1H, m), 7.62 (1H, d, J=9.62 Hz), 7.64-7.71 (1H, m), 8.45-8.50 (1H, m);

Mass (ESI): 675 $(2M+Na)^+$, 349 $(M+Na)^+$, 327 $(M+H)^+$;

Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17.

Found: C, 66.41; H, 7.06; N, 17.16.

Preparation 61

6-[2-(1-Hydroxy-1,2-dimethylpropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 138.5-140°C (acetone-isopropyl ether);

IR (KBr): 3313, 1646, 1583, 1529 cm^{-1};

^1H NMR ($CDCl_3$, δ): 0.72 (3H, d, J=6.86 Hz), 1.07 (3H, d, J=6.76 Hz), 1.41 (3H, d, J=6.74 Hz), 1.46 (3H, d, J=6.72 Hz), 1.63 (3H, s), 2.05-2.32 (1H, m), 4.96 (1H, s), 5.46 (1H, 7-plet, J=6.72 Hz), 6.8-6.9 (1H, m), 7.05 (1H, d, J=9.58 Hz), 7.19-7.29 (1H, m), 7.47-7.57 (2H, m), 8.44-8.50 (1H, m);

Mass (ESI): 703 $(2M+Na)^+$, 363 $(M+Na)^+$, 341 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46.
Found: C, 67.02; H, 7.33; N, 16.38.

Example 7

In the presence of Nafion® NR50 (75 mg), a solution of 6-[2-(1-hydroxycyclobutyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (62 mg) in glacial acetic acid (1.2 mL) was refluxed for 20 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 5:5 v/v) to give 6-[2-(1-cyclobuten-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (15 mg).

mp: 124.5-126°C (acetone-hexane);

IR (KBr): 1662, 1591 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.61 Hz), 2.6-2.7 (2H, m), 2.99-3.04 (2H, m), 5.43 (1H, 7-plet, J=6.61 Hz), 6.32 (1H, s), 6.8-6.92 (1H, m), 6.96 (1H, d, J=9.55 Hz), 7.15-7.3 (1H, m), 7.64 (1H, d, J=9.57 Hz), 7.77 (1H, d, J=9.11 Hz), 8.46 (1H, d, J=6.96 Hz);

Mass (APCI): 307 $(M+H)^+$, 265;

Anal. Calcd for $C_{18}H_{18}N_4O \cdot 0.2H_2O$: C, 69.75; H, 5.98; N, 18.08.
Found: C, 69.82; H, 5.92; N, 18.08.

The following compounds of Examples 8 to 17 were prepared in a similar manner to Example 7.

Example 8

6-[2-(1-Cyclohepten-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 118-120°C (hexane);

IR (KBr): 1660, 1587, 1527 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.48 (6H, d, J=6.63 Hz), 1.5-1.9 (6H, m), 2.25-2.4 (2H, m), 2.6-2.7 (2H, m), 5.43 (1H, 7-plet, J=6.63 Hz), 6.23 (1H, t, J=6.49 Hz), 6.75-6.9 (1H, m), 6.91 (1H, d, J=9.60 Hz), 7.15-7.3 (1H, m), 7.49 (1H, d, J=9.61 Hz), 7.91 (1H, d, J=8.92 Hz), 8.44 (1H, d, J=6.95 Hz);

Mass (ESI): 719 $(2M+Na)^+$, 371 $(M+Na)^+$, 349 $(M+H)^+$;

Anal. Calcd for $C_{21}H_{24}N_4O \cdot 0.2H_2O$: C, 71.64; H, 6.98; N, 15.91.

Found: C, 71.70; H, 7.04; N, 15.81.

Example 9

6-[2-(1-Cycloocten-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 131.5-132.5°C (hexane);

IR (KBr): 1660, 1587, 1527 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.48 (6H, d, J=6.64 Hz), 1.5-1.8 (8H, m), 2.2-2.35 (2H, m), 2.55-2.65 (2H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 6.05 (1H, t, J=8.25 Hz), 6.75-6.87 (1H, m), 6.89 (1H, d, J=9.61 Hz), 7.15-7.3 (1H, m), 7.51 (1H, d, J=9.61 Hz), 7.90 (1H, d, J=8.94 Hz), 8.46 (1H, d, J=6.96 Hz);

Mass (AESI): 747 $(2M+Na)^+$, 385 $(M+Na)^+$, 363 $(M+H)^+$;

Anal. Calcd for $C_{22}H_{26}N_4O \cdot 0.1H_2O$: C, 72.18; H, 7.27; N, 15.30.

Found: C, 72.35; H, 7.36; N, 15.30.

Example 10

2-Isopropyl-6-[2-(6-methyl-1-cyclohexen-1-yl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (72 mg) was prepared as a syrup from the less polar stereoisomer of 6-[2-(1-hydroxy-2-methylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (100 mg).

IR (Neat): 1660, 1587, 1529 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.00 (3H, d, J=7.03 Hz), 1.43 (3H, d, J=6.70 Hz), 1.51 (3H, d, J=6.60 Hz), 1.4-3.0 (7H, m), 5.43 (1H, 7-plet, J=6.62 Hz), 5.95-6.0 (1H, m), 6.8-6.9 (1H, m), 6.90 (1H, d, J=9.59 Hz), 7.2-7.3 (1H, m), 7.53 (1H, d, J=9.62 Hz), 7.97 (1H, d, J=8.92 Hz), 8.45 (1H, d, J=6.95 Hz);

Mass (ESI): 719 $(2M+Na)^+$, 371 $(M+Na)^+$, 349 $(M+H)^+$, 281.

Example 11

2-Isopropyl-6-[2-(6-methyl-1-cyclohexen-1-yl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (70 mg) was prepared as a syrup from the more polar stereoisomer of 6-[2-(1-hydroxy-2-methylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone).

mp: 131.5-133°C (isopropyl ether-hexane)

IR (Neat): cm^{-1}; 1662, 1587, 1527 cm^{-1};

Mass (ESI): 719 $(2M+Na)^+$, 371 $(M+Na)^+$, 349 $(M+H)^+$;

^1H NMR ($CDCl_3$, δ): 1.04 (3H, d, J=6.01 Hz), 1.1-2.5 (7H, m), 1.47 (3H, d, J=6.63 Hz), 1.48 (3H, d, J=6.63 Hz), 5.43 (6H, 7-plet, J=6.63 Hz), 6.0-6.05 (1H, m), 6.8-6.9 (1H, m), 6.91 (1H, d, J=9.62 Hz), 7.2-7.3 (1H, m), 7.46 (1H, d, J=9.62 Hz), 7.93 (1H, d, J=8.95 Hz), 8.44 (1H, d, J=6.96 Hz);

Mass (ESI): 719 $(2M+Na)^+$, 371 $(M+Na)^+$, 349 $(M+H)^+$.

Example 12

2-Isopropyl-6-[2-(4-methyl-1-cyclohexen-1-yl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (10 mg) was prepared as a solid from the less polar stereoisomer of 6-[2-(1-hydroxy-4-methylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (35 mg).

mp: 131.5-133°C (isopropyl ether-hexane);

IR (KBr): 1662, 1587, 1527 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.04 (3H, d, J=6.01 Hz), 1.1-2.5 (7H, m), 1.47 (3H, d, J=6.63 Hz), 1.48 (3H, d, J=6.63 Hz), 5.43 (6H, 7-plet, J=6.63 Hz), 6.0-6.05 (1H, m), 6.8-6.9 (1H, m), 6.91 (1H, d, J=9.62 Hz), 7.2-7.3 (1H, m), 7.46 (1H, d, J=9.62 Hz), 7.93 (1H, d, J=8.95 Hz), 8.44 (1H, d, J=6.96 Hz);

Mass (ESI): 719 $(2M+Na)^+$, 371 $(M+Na)^+$, 349 $(M+H)^+$.

Example 13

2-Isopropyl-6-[2-(4-methyl-1-cyclohexen-1-yl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (71 mg) was prepared as a solid from the more polar stereoisomer of 6-[2-(1-hydroxy-4-methylcyclohexyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (100 mg).
mp: 131.5-133°C (isopropyl ether-hexane);
IR (KBr): 1662, 1587, 1527 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.04 (3H, d, J=6.01 Hz), 1.1-2.5 (7H, m), 1.47 (3H, d, J=6.63 Hz), 1.48 (3H, d, J=6.63 Hz), 5.43 (6H, 7-plet, J=6.63 Hz), 6.0-6.05 (1H, m), 6.8-6.9 (1H, m), 6.91 (1H, d, J=9.62 Hz), 7.2-7.3 (1H, m), 7.46 (1H, d, J=9.62 Hz), 7.93 (1H, d, J=8.95 Hz), 8.44 (1H, d, J=6.96 Hz);
Mass (ESI): 719 $(2M+Na)^+$, 371 $(M+Na)^+$, 349 $(M+H)^+$.

Example 14

6-[2-(4,4-Dimethyl-1-cyclohexen-1-yl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 127.5-129°C (hexane);
IR (KBr): 1658, 1587, 1527 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.02 (6H, s), 1.48 (6H, d, J=6.64 Hz), 1.45-1.6 (2H, m), 1.95-2.05 (2H, m), 2.4-2.5 (2H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 5.95-6.02 (1H, m), 6.75-6.9 (1H, m), 6.90 (1H, d, J=9.57 Hz), 7.2-7.3 (1H, m), 7.44 (1H, d, J=9.60 Hz), 7.91 (1H, d, J=8.94 Hz), 8.45 (1H, d, J=6.94 Hz);
Mass (ESI): 747 $(2M+Na)^+$, 385 $(M+Na)^+$, 353 $(M+H)^+$.

Example 15

2-Isopropyl-6-[2-(2-methyl-2,5-dihydro-3-furanyl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone
^1H NMR ($CDCl_3$, δ): 1.44 (6H, d, J=6.46 Hz), 1.49 (3H, d, J=6.64 Hz), 4.7-4.95 (2H, m), 5.35-5.55 (2H, m), 6.11-6.16 (1H, m), 6.83-6.92 (1H, m), 6.97 (1H, d, J=9.58 Hz), 7.2-7.32 (1H, m), 7.48 (1H, d, J=9.58 Hz), 7.80 (1H, d, J=8.94 Hz), 8.45 (1H, d, J=6.96 Hz);
Mass (APCI): 337 $(M+H)^+$.

Example 16

6-[2-(3,6-Dihydro-2H-pyran-4-yl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 134.5-136°C (hexane);
IR (KBr): 1660, 1587, 1529 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.66 Hz), 2.6-2.7 (2H, m), 3.9-4.0 (2H, m), 4.25-4.35 (2H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 6.05-6.1 (1H, m), 6.8-7.0 (2H, m), 7.2-7.3 (1H, m), 7.47 (1H, d, J=9.60 Hz), 7.8-7.9 (1H, m), 8.4-8.5 (1H, m);
Mass (APCI): 337 $(M+H)^+$.

Example 17

6-[2-(3,6-Dihydro-2H-thiopyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 165-166°C (acetone);
IR (KBr): 1658, 1587, 1529 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.48 (6H, d, J=6.64 Hz), 2.75-2.81 (2H, m), 2.87-2.95 (2H, m), 3.28-3.34 (2H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 6.15-6.21 (1H, m), 6.8-6.9 (1H, m), 6.94 (1H, d, J=9.64 Hz), 7.22-7.31 (1H, m), 7.93 (1H, d, J=8.94 Hz), 8.43 (1H, d, J=6.95 Hz);
Mass (ESI): 727 $(2M+Na)^+$, 375 $(M+Na)^+$, 353 $(M+H)^+$.

Example 18

In the presence of Nafion® NR50 (150 mg), a solution of 6-[2-(1-hydroxypropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (60 mg) in xylene (3 mL) was refluxed for 40 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 1:2 v/v) to give 2-isopropyl-6-[2-((1E)-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (29 mg).
mp: 145-147°C (hexane);
IR (KBr): 1658, 1585 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 1.95-2.0 (3H, m), 5.44 (1H, 7-plet, J=6.63 Hz), 6.59-6.70 (2H, m), 6.75-6.88 (1H, m), 6.99 (1H, d, J=9.58 Hz), 7.18-7.27 (1H, m), 7.51

(1H, d, J=9.58 Hz), 7.77-7.83 (1H, m), 8.41-8.47 (1H, m);
Mass (APCI): 295 $(M+H)^+$, 253;
Anal. Calcd for $C_{27}H_{28}N_4O \cdot 0.1H_2O$: C, 68.94; H, 6.19; N, 18.92.
Found: C, 68.98; H, 6.07; N, 18.75.

The following compound of Example 19 was prepared in a similar manner to Example 18.

Example 19

2-Isopropyl-6-[2-(2-methyl-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone
mp: 73-74°C (isopropyl ether-hexane);
IR (KBr): 1662, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.62 Hz), 1.97 (3H, d, J=1.10 Hz), 2.00 (3H, d, J=1.28 Hz), 5.44 (1H, 7-plet, J=6.63 Hz), 6.36-6.38 (1H, m), 6.78-6.88 (1H, m), 6.95 (1H, d, J=9.60 Hz), 7.2-7.3 (1H, m), 7.59 (1H, d, J=9.62 Hz), 7.93-7.99 (1H, m), 8.43-8.48 (1H, m);
Mass (APCI): 311 $(M+H)^+$, 252;
Anal. Calcd for $C_{18}H_{20}N_4O \cdot 0.1H_2O$: C, 69.70; H, 6.56; N, 18.06.
Found: C, 69.78; H, 6.49; N, 17.99.

Example 20

In the presence of Nafion® NR50 (300 mg), a solution of 6-[2-(1-hydroxy-1-methylpropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (120 mg) in xylene (6 mL) was refluxed for 40 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 5:5 v/v) to give 2-isopropyl-6-{2-[(1E or 1Z)-1-methyl-1-propenyl]pyrazolo-[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone as a solid (66 mg).
mp: 101-102°C (hexane);
IR (KBr): 1662, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.48 (6H, d, J=6.64 Hz), 1.83 (3H, dd, J=0.95, 6.88 Hz), 2.08-2.12 (3H, m), 5.43 (1H, 7-plet, J=6.64 Hz), 5.85-5.90 (1H, m), 6.80-6.88 (1H, m), 6.90 (1H, d, J=9.64 Hz), 7.20-7.29 (1H, m), 7.43 (1H, d, J=9.64 Hz), 7.90-7.96 (1H, m), 8.41-8.46 (1H, m);

Mass (APCI): 309 $(M+H)^+$, 267;
Anal. Calcd for $C_{18}H_{20}N_4O \cdot 0.2H_2O$: C, 69.30; H, 6.59; N, 17.96.
Found: C, 69.36; H, 6.59; N, 17.75.

Example 21

In the presence of Nafion® NR50 (250 mg), a solution of 6-[2-(1-hydroxy-1,2-dimethylpropyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (100 mg) in xylene (5 mL) was refluxed for 40 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 5:5 v/v) to give two products. A less polar one was 2-isopropyl-6-[2-(1-isopropylvinyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (33 mg) and a more polar one was 2-isopropyl-6-[2-(1,2-dimethyl-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (27 mg).

(1) 2-Isopropyl-6-[2-(1,2-dimethyl-1-propenyl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone
IR (Neat): 1658, 1585 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 1.56 (3H, d, J=1.42 Hz), 1.90 (3H, s), 2.04 (3H, s), 5.44 (1H, 7-plet, J=6.63 Hz), 6.86-6.91 (1H, m), 6.90 (1H, d, J=9.66 Hz), 7.24-7.30 (1H, m), 7.51 (1H, d, J=9.68 Hz), 8.11-8.17 (1H, m), 8.43-8.48 (1H, m);
Mass (APCI): 323 $(M+H)^+$, 281.

(2) 2-Isopropyl-6-[2-(1-isopropylvinyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone
mp: 86-87.5°C (hexane);
IR (KBr): 1658, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.17 (6H, d, J=6.82 Hz), 1.48 (6H, d, J=6.64 Hz), 2.87 (1H, 7-plet, J=6.76 Hz), 5.26 (1H, s), 5.40 (1H, s), 5.43 (1H, 7-plet, J=6.64 Hz), 6.83-6.92 (1H, m), 6.89 (1H, d, J=9.66 Hz), 7.2-7.32 (1H, m), 7.51 (1H, d, J=9.60 Hz), 7.95-8.01 (1H, m), 8.43-8.49(1H, m);
Mass (APCI): 323$(M+H)^+$, 281;
Anal. Calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38.

Found C, 70.54; H, 7.03; N, 17.08.

Example 22

6-[2-(1-Ethyl-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (E,Z-mixture)

mp: 110.5-112.5°C (hexane);

IR (KBr): 1660, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.04 (3H, t, J=7.55 Hz), 1.48 (6H, d, J=6.64 Hz), 1.83 (3H, d, J=6.94 Hz), 2.57 (2H, q, J=7.52 Hz), 5.43 (1H, 7-plet, J=6.64 Hz), 5.77 (1H, q, J=6.92 Hz), 6.83-6.93 (2H, m), 7.24-7.30 (1H, m), 7.48 (1H, d, J=9.66 Hz), 7.92-8.00 (1H, m), 8.42-8.47 (1H, m) (data of the major isomer);

Mass (APCI): 323 $(M+H)^+$, 281;

Anal. Calcd for $C_{19}H_{22}N_4O \cdot 0.2H_2O$: C, 70.00; H, 6.92; N, 17.18.

Found: C, 69.98; H, 6.83; N, 17.15.

Preparation 62

Below -65°C, 1.52N butyllithium solution in hexane (52 mL) was added dropwise to a solution of ethynyl(trimethyl)silane (11.09 mL) in tetrahydrofuran (120 mL). After 0.5 hour, cyclobutanone (5.0 g) was added dropwise at the same temperature. The mixture was stirred at the same temperature for 0.5 hour and allowed to warm to ambient temperature over 2 hours. The mixture was cooled to below -65°C, and a mixture of saturated aqueous ammonium chloride solution (80 mL) and water (80 mL) was added and allowed to warm to ambient temperature. The mixture was extracted with ethyl ether, dried over magnesium sulfate, and concentrated at atmospheric pressure to give an oil. The oil was distilled at atmospheric pressure to give 1-[2-(trimethylsilyl)-1-ethynyl]cyclobutanol (11.37 g).

bp: 166-169°C;

IR (Neat): 3350-3300, 2165 cm^{-1};

^1H NMR ($CDCl_3$, δ): 0.19 (9H, s), 1.77-1.87 (2H, m), 2.2-2.5 (5H, m);

Mass (ESI): 191 $(M+Na)^+$.

Preparation 63

Under ice-cooling, 1M tetrabutylammonium fluoride solution in tetrahydrofuran (63 mL) was added to a solution of 1-[2-(trimethylsilyl)-1-ethynyl]cyclobutanol (10.45 g) in tetrahydrofuran (10 mL). The mixture was stirred at the same temperature for 0.5 hour and at ambient temperature for 0.5 hour and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 5:5 v/v) to give 1-ethynylcyclobutanol as an oil (4.84 g).

IR (Neat): 3390-3290, 2115 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.78-1.88 (2H, m), 2.20-2.25 (4H, m), 2.28 (1H, s), 2.54 (1H, s);

^1H NMR (DMSO-d_6, δ): 1.6-1.8 (2H, m), 2.0-2.3 (4H, m), 3.31 (1H, s), 5.72 (1H, s).

Preparation 64

Phosphorus pentoxide (25 g) was added to 2-propyn-1-ol (500 mL) and dimethoxymethane (100 g) in dichloromethane (500 mL) was added dropwise. The mixture was stirred at ambient temperature for 14 hours. Then, phosphorus pentoxide (25 g) was added and the mixture was stirred at ambient temperature for 20 hours. The mixture was poured into a mixture of sodium carbonate and ice-water, extracted with chloroform, dried over magnesium sulfate, and concentrated at atmospheric pressure to give an oil. The oil was distilled at atmospheric pressure to give 3-(methoxymethoxy)-1-propyne as an oil (103 g).

bp: 106-109°C;

IR (Neat): 3293, 2119 cm^{-1};

^1H NMR ($CDCl_3$, δ): 2.43 (1H, t, J=2.42 Hz), 3.39 (3H, s), 4.22 (2H, d, J=2.42 Hz), 4.73 (2H, s).

Preparation 65

Below -65°C, 1.6N butyllithium solution in hexane (53.5 mL) was added dropwise to a solution of 3-(methoxymethoxy)-1-propyne (7.75 g) in tetrahydrofuran (150 mL). After 0.5 hour, N-methoxy-N-methylacetamide (8.0 mL) was added dropwise at the same temperature. The mixture was

stirred at the same temperature for 0.5 hour and allowed to warm to ambient temperature over 0.5 hour. Below -65°C, 4N hydrochloric acid (39 mL) was added and allowed to warm to ambient temperature. The mixture was extracted with ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure to give an oil. The oil was purified by column chromatography on silica gel (hexane-ethyl acetate 9:1 v/v) to give 5-(methoxymethoxy)-3-pentyn-2-one as an oil (7.57 g).

^{1}H NMR ($CDCl_3$, δ): 2.36 (3H, s), 3.40 (3H, s), 4.38 (2H, s), 4.71 (2H, s).

Preparation 66

A solution of 1-aminopyridinium iodide (17.68 g), sodium hydroxide (6.37 g) and benzyltriethylammonium chloride (1.18 g) in water (40 mL) was stirred at ambient temperature for 0.5 hour. To the solution was added dichloromethane (40 mL) and, then, a solution of 5-(methoxymethoxy)-3-pentyn-2-one (7.55 g) in dichloromethane (40 mL) under ice-cooling. The mixture was stirred at the same temperature for 4 hours, extracted with dichloromethane, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 6:4 v/v) to give 1-{2-[(methoxymethoxy)methyl]pyrazolo[1,5-a]pyridin-3-yl}ethanone as a solid (8.21 g).

mp: 70-71°C (isopropyl ether-hexane);

IR (KBr): 1655, 1627, 1514 cm^{-1};

^{1}H NMR (DMSO-d_6, δ): 2.60 (3H, s), 3.33 (3H, s), 4.71 (2H, s), 4.93 (2H, s), 7.14-7.22 (1H, m), 7.58-7.67 (1H, m), 8.22 (1H, d, J=8.92 Hz), 8.84 (1H, d, J=6.87 Hz);

Mass (ESI): 491 $(2M+Na)^+$, 257 $(M+Na)^+$;

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96.
Found: C, 61.77; H, 6.12; N, 12.00.

Preparation 67

A mixture of 1-{2-[(methoxymethoxy)methyl]pyrazolo-

[1,5-a]pyridin-3-yl}ethanone (1.40 g) and glyoxylic acid monohydrate (1.66 g) in 1,2-dimethoxyethane (6 mL) was refluxed for 50 hours. The mixture was concentrated under reduced pressure and dissolved in 28% aqueous ammonia solution (29 mL). Hydrazine monohydrate (2.9 mL) was added and the mixture was refluxed for 8 hours. After ice-cooling, the insoluble solid was collected by filtration and dried under reduced pressure to give 6-[2-(hydroxymethyl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone as a solid (0.73 g).

mp: 240-242°C;

IR (KBr): 3491, 1697, 1590 cm^{-1};

^{1}H NMR (DMSO-d_6, δ): 4.76 (2H, d, J=5.46 Hz), 5.49 (1H, t, J=5.47 Hz), 6.97-7.06 (2H, m), 7.35-7.44 (1H, m), 7.97-8.04 (2H, m), 8.72 (1H, d, J=6.94 Hz), 13.07 (1H, br. s);

Mass (APCI): 243 $(M+H)^+$;

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13.
Found: C, 59.25; H, 4.06; N, 22.8.

Preparation 68

Imidazole (0.55 g) was added to a mixture of 6-[2-(hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (1.51 g) and tert-butyldimethylchlorosilane (1.03 g) in dimethylformamide (6 mL) and the mixture was stirred at ambient temperature for 2 hours. The mixture was poured into ice-water, extracted with ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure to give a solid. The solid was recrystallized from a mixture of ethyl acetate and isopropyl ether to give 6-{2-{[(tert-butyldimethylsilyl)oxy]methyl}pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone (1.80 g).

mp: 160-162°C (ethyl acetate-isopropyl ether);

IR (KBr): 1680, 1595 cm^{-1};

^{1}H NMR (DMSO-d_6, δ): 0.02 (6H, s), 0.79 (9H, s), 4.99 (2H, s), 6.95-7.05 (2H, m), 7.35-7.43 (1H, m), 7.88-7.98 (2H, m), 8.73 (1H, d, J=6.94 Hz), 13.09 (1H, br. s);

Mass (APCI): 357 $(M+H)^+$;

Anal. Calcd for $C_{16}H_{24}N_4O_2Si$: C, 60.64; H, 6.79; N, 15.72.
Found: C, 60.71; H, 6.94; N, 15.76.

Preparation 69

A mixture of 6-{2-{[(tert-butyldimethylsilyl)oxy]-methyl}pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone (2.01 g) and sodium hydride (60% oil suspension) (0.24 g) in dimethylformamide (10 mL) was heated at 55-60°C for 0.5 hour. Isopropyl iodide (0.6 mL) was added to the mixture at ambient temperature. After stirring at ambient temperature for 12 hours and at 55-60°C for an hour, the mixture was poured into ice-water, extracted with ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure to give a syrup. The syrup was purified by column chromatography on silica gel (hexane-ethyl acetate 6:4 v/v) to give 6-{2-{[(tert-butyldimethylsilyl)oxy]methyl}-pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone as a solid (2.01 g).
mp: 100-101°C (isopropyl ether-hexane);
IR (KBr): 1664, 1595 cm^{-1};
^1H NMR (DMSO-d_6, δ): 0.02 (6H, s), 0.78 (9H, s), 1.37 (6H, d, J=6.63 Hz), 5.01 (2H, s), 5.26 (1H, 7-plet, J=6.63 Hz), 6.97-7.06 (2H, m), 7.39-7.48 (1H, m), 7.90 (1H, d, J=9.68 Hz), 8.00 (1H, d, J=8.94 Hz), 8.75 (1H, d, J=6.95 Hz);
Mass (APCI): 399 $(M+H)^+$;
Anal. Calcd for $C_{21}H_{30}N_4O_2$: C, 63.28; H, 7.59; N, 14.06.
Found: C, 63.48; H, 7.62; N, 14.18.

Preparation 70

A solution of 6-{2-{[(tert-butyldimethylsilyl)-oxy]methyl}pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone (2.00 g) in a mixture of concentrated hydrochloric acid (0.2 mL) and methanol (2 mL) was stirred at ambient temperature for 3 hours. The mixture was concentrated under reduced pressure, triturated with ethyl acetate, collected by filtration, and dried under reduced pressure to give 6-[2-(hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (1.29 g).

mp: 153.5-154.5°C (chloroform-isopropyl ether);
IR (KBr): 3222, 1670, 1600 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.39 (6H, d, J=6.62 Hz), 4.79 (2H, s), 5.27 (1H, 7-plet, J=6.62 Hz), 6.01 (1H, br. s), 7.00-7.07 (2H, m), 7.40-7.49 (1H, m), 7.98-8.09 (2H, m), 8.74 (1H, d, J=6.94 Hz);
Mass (APCI): 285 $(M+H)^+$;
Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71.
Found: C, 63.10; H, 5.54; N, 19.58.

Preparation 71

Thionyl chloride (3.77 mL) was added to a solution of 6-[2-(hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (11.30 g) in dichloroethane (38 mL) and the mixture was heated under reflux for 4 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was washed with saturated aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a solid. The solid was crystallized from a mixture of chloroform and hexane to give 6-[2-(chloromethyl)-pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (11.14 g).
mp: 187.5-188.5°C (chloroform-hexane);
IR (KBr): 1658, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 4.97 (2H, s), 5.45 (1H, 7-plet, J=6.63 Hz), 6.87-6.96 (1H, m), 7.05 (1H, d, J=9.60 Hz), 7.26-7.35 (1H, m), 7.66 (1H, d, J=9.60 Hz), 7.84 (1H, d, J=9.01 Hz), 8.48 (1H, d, J=6.98 Hz);
Mass (APCI): 305 and 303 $(M+H)^+$;
Anal. Calcd for $C_{15}H_{15}ClN_4O$: C, 59.51; H, 4.99; N, 18.51.
Found: C, 59.26; H, 4.94; N, 18.38.

Preparation 72

A mixture of 6-[2-(chloromethyl)pyrazolo[1,5-a]-pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (5.06 g) and triethyl phosphite (4.3 mL) was heated under refluxed for 6 hours. After cooling, the mixture was triturated with

isopropyl ether, collected by filtration, and dried under reduced pressure to give diethyl [3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyrazinyl)pyrazolo[1,5-a]pyridin-2-yl]-methylphosphonate (6.51 g).

mp: 129.5-130.5°C (isopropyl ether);

IR (KBr): 1658, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.25 (6H, t, J=7.06 Hz), 1.45 (6H, d, J=6.63 Hz), 3.68 (2H, d, J=21.38 Hz), 4.0-4.2 (4H, m), 5.44 (1H, 7-plet, J=6.63 Hz), 6.85 (1H, t, J=6.40 Hz), 7.02 (1H, d, J=9.59 Hz), 7.25 (1H, m), 7.74 (2H, d, J=9.59 Hz), 8.46 (1H, d, J=6.97 Hz);

Mass (APCI): 405 $(M+H)^+$;

Anal. Calcd for $C_{19}H_{25}N_4O_4P$: C, 56.43; H, 6.23; N, 13.85.
Found: C, 56.28; H, 6.24; N, 13.81.

Example 23

A suspension of diethyl [3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyrazinyl)pyrazolo[1,5-a]pyridin-2-yl]-methylphosphonate (99.7 mg) and sodium hydride (60% oil suspension) (10.8 mg) in dioxane (1 mL) was heated at 55-60°C for an hour under nitrogen atmosphere. Acetaldehyde (0.5 mL) was added to the mixture under ice-cooling and the mixture was stirred at the same temperature for an hour and at ambient temperature for 20 hours. The reaction mixture was poured into a mixture of water and chloroform. The organic layer was collected, dried over magnesium sulfate, and concentrated under reduced pressure to give a syrup. The syrup was purified by preparative TLC on silica gel (hexane-ethyl acetate 5:5 v/v) to give 2-isopropyl-6-{2-[(1E)-1-propenyl]pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone as a solid (21.6 mg).

mp: 145-147°C (hexane);

IR (KBr): 1658, 1585 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 1.95-2.0 (3H, m), 5.44 (1H, 7-plet, J=6.63 Hz), 6.59-6.70 (2H, m), 6.75-6.88 (1H, m), 6.99 (1H, d, J=9.58 Hz), 7.18-7.27 (1H, m), 7.51 (1H, d, J=9.58 Hz), 7.77-7.83 (1H, m), 8.41-8.47 (1H, m);

Mass (APCI): 295 $(M+H)^+$, 253;

Anal. Calcd for $C_{27}H_{26}N_4O \cdot 0.1H_2O$: C, 68.94; H, 6.19; N, 18.92.
Found: C, 68.98; H, 6.07; N, 18.75.

The following compounds of Examples 24 to 47 were prepared in a similar manner to Example 23.

Example 24

2-Isopropyl-6-[2-(2-methyl-1-propenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone

mp: 73-74°C (isopropyl ether-hexane)

IR (KBr): 1662, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.62 Hz), 1.97 (3H, d, J=1.10 Hz), 2.00 (3H, d, J=1.28 Hz), 5.44 (1H, 7-plet, J=6.63 Hz), 6.36-6.38 (1H, m), 6.78-6.88 (1H, m), 6.95 (1H, d, J=9.60 Hz), 7.2-7.3 (1H, m), 7.59 (1H, d, J=9.62 Hz), 7.93-7.99 (1H, m), 8.43-8.48 (1H, m);

Mass (APCI): 311 $(M+H)^+$, 252;

Anal. Calcd for $C_{18}H_{20}N_4O \cdot 0.1H_2O$: C, 69.70; H, 6.56; N, 18.06.
Found: C, 69.78; H, 6.49; N, 17.99.

Example 25

6-[2-(2-Ethyl-1-butenyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone

mp: 70-74°C;

IR (KBr): 1662, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.00 (3H, t, J=7.53 Hz), 1.17 (3H, t, J=7.42 Hz), 1.47 (6H, d, J=6.63 Hz), 2.27 (2H, q, J=7.40 Hz), 2.41 (2H, q, J=7.53 Hz), 5.44 (1H, 7-plet, J=6.64 Hz), 6.30 (1H, s), 6.75-6.9 (1H, m), 6.93 (1H, d, J=9.62 Hz), 7.2-7.3 (1H, m), 7.61 (1H, d, J=9.62 Hz), 7.97 (1H, d, J=8.96 Hz), 8.46 (1H, d, J=6.94 Hz);

Mass (APCI): 337 $(M+H)^+$.

Example 26

6-{2-[(E)-2-Cyclopropylethenyl]pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone

mp: 127-128°C (isopropyl ether);

IR (KBr): 1662, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 0.55-0.65 (2H, m), 0.8-0.95 (2H, m), 1.47

(6H, d, J=6.63 Hz), 1.5-1.7 (1H, m), 5.45 (1H, 7-plet, J=6.63 Hz), 6.21 (1H, dd, J=9.41, 15.62 Hz), 6.72 (1H, d, J=15.62 Hz), 6.75-6.9 (1H, m), 7.00 (1H, d, J=9.58 Hz), 7.15-7.3 (1H, d), 7.53 (1H, d, J=9.58 Hz), 7.78 (1H, d, J=8.91 Hz), 8.43 (1H, d, J=6.94 Hz);
Mass (APCI): 321 $(M+H)^+$.

Example 27

6-[2-(Cyclobutylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 130-132.5°C (acetone-hexane)
IR (KBr): 1652, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.63 Hz), 2.09 (2H, 5-plet, J=7.69 Hz), 2.85-3.0 (2H, m), 3.0-3.1 (2H, m), 5.44 (1H, 7-plet, J=6.63 Hz), 6.3-6.4 (1H, m), 6.75-6.85 (1H, m), 6.98 (1H, d, J=9.59 Hz), 7.15-7.3 (1H, m), 7.54 (1H, d, J=9.59 Hz), 7.82 (1H, d, J=8.94 Hz), 8.43 (1H, d, J=6.95 Hz);
Mass (APCI): 321 $(M+H)^+$;
Anal. Calcd for $C_{19}H_{20}N_4O \cdot 0.2H_2O$: C, 70.44; H, 6.35; N, 17.29.
Found: C, 70.48; H, 6.24; N, 17.01.

Example 28

6-[2-(Cyclopentylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
IR (KBr): 1660, 1581 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.60 Hz), 1.65-1.85 (4H, m), 2.5-2.6 (2H, m), 2.6-2.7 (2H, m), 5.44 (1H, 7-plet, J=6.60 Hz), 6.55 (1H, br. s), 6.75-6.85 (1H, m), 6.98 (1H, d, J=9.59 Hz), 7.15-7.3 (1H, m), 7.57 (1H, d, J=9.60 Hz), 7.85 (1H, d, J=8.95 Hz), 8.46 (1H, d, J=6.92 Hz);
Mass (APCI): 335 $(M+H)^+$.

Example 29

6-[2-(Cyclohexylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 130-131.5°C (hexane);
IR (KBr): 1662, 1590 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.45-1.75 (6H, m), 1.47 (6H, 7-plet, J=6.63 Hz), 2.3-2.4 (2H, m), 2.4-2.5 (2H, m), 5.44 (1H, 7-

plet, J=6.63 Hz), 6.31 (1H, s), 6.75-6.9 (1H, m), 6.94 (1H, d, J=9.63 Hz), 7.2-7.3 (1H, m), 7.63 (1H, d, J=9.62 Hz), 7.96 (1H, d, J=8.96 Hz), 8.45 (1H, d, J=6.95 Hz);
Mass (APCI): 349 $(M+H)^+$;
Anal. Calcd for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08.
Found: C, 72.44; H, 6.80; N, 15.84.

Example 30

6-[2-(Cycloheptylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 1662, 1633, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.62 Hz), 1.4-1.8 (8H, m), 2.45-2.55 (2H, m), 2.6-2.7 (2H, m), 5.44 (1H, 7-plet, J=6.62 Hz), 6.38 (1H, br. s), 6.75-6.9 (1H, m), 6.96 (1H, d, J=9.61 Hz), 7.2-7.3 (1H, m), 7.62 (1H, d, J=9.62 Hz), 7.94 (1H, d, J=8.93 Hz), 8.46 (1H, d, J=6.93 Hz);
Mass (APCI): 363 $(M+H)^+$.

Example 31

6-[2-(Cyclooctylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone
IR (Neat): 1664, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.4-1.85 (10H, m), 1.47 (6H, d, J=6.63 Hz), 2.4-2.5 (2H, m), 2.6-2.7 (2H, m), 5.44 (1H, 7-plet, J=6.62 Hz), 6.41 (1H, s), 6.75-6.85 (1H, m), 6.95 (1H, d, J=9.60 Hz), 7.15-7.3 (1H, m), 7.57 (1H, d, J=9.60 Hz), 7.90 (1H, d, J=8.94 Hz), 8.46 (1H, d, J=6.95 Hz);
Mass (APCI): 377 $(M+H)^+$.

Example 32

2-Isopropyl-6-{2-[(2-methylcyclohexylidene)methyl]-pyrazolo-[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone (E,Z-mixture)
IR (Neat): 1664, 1633, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 5.44 (6H, 7-plet, J=6.63 Hz);
Mass (APCI): 363 $(M+H)^+$.

Example 33

2-Isopropyl-6-{2-[(4-methylcyclohexylidene)methyl]-pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone

IR (KBr): 1664, 1635, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.85-2.05 (6H, m), 0.92 (3H, d, J=6.36 Hz), 1.46 (3H, d, J=6.54 Hz), 1.48 (3H, d, J=6.45 Hz), 2.2-2.5 (2H, m), 2.95-3.1 (1H, m), 5.44 (1H, 7-plet, J=6.60 Hz), 6.32 (1H, s), 6.8-6.9 (1H, m), 6.95 (1H, d, J=9.62 Hz), 7.2-7.3 (1H, m), 7.63 (1H, d, J=9.62 Hz), 7.97 (1H, d, J=8.92 Hz), 8.45 (1H, d, J=6.91 Hz);
Mass (APCI): 363 $(M+H)^+$.

Example 34

2-Isopropyl-6-[2-(tetrahydro-4H-pyran-4-ylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone
mp: 156-157.5°C (acetone-hexane);
IR (KBr): 1662, 1590 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 2.45-2.55 (2H, m), 2.7-2.8 (2H, m), 3.65-3.75 (2H, m), 3.8-3.9 (2H, m), 5.45 (1H, 7-plet, J=6.62 Hz), 6.43 (1H, br. s), 6.8-6.9 (1H, m), 6.98 (1H, d, J=9.61 Hz), 7.2-7.3 (1H, m), 7.57 (1H, d, J=9.61 Hz), 7.90 (1H, d, J=8.92 Hz), 8.45 (1H, d, J=6.96 Hz);
Mass (APCI): 351 $(M+H)^+$;
Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 67.51; H, 6.40; N, 15.75.
Found: C, 67.52; H, 6.20; N, 15.67.

Example 35

2-Isopropyl-6-[2-(tetrahydro-4H-thiopyran-4-ylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone
mp: 165.5-166.5°C (acetone);
IR (KBr): 1660, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 2.65-2.75 (4H, m), 2.75-2.85 (2H, m), 2.9-2.95 (2H, m), 5.44 (1H, 7-plet, J=6.62 Hz), 6.41 (1H, s), 6.8-6.9 (1H, m), 6.97 (1H, d, J=9.61 Hz), 7.2-7.3 (1H, m), 7.56 (1H, d, J=9.61 Hz), 7.93 (1H, d, J=8.95 Hz), 8.45 (1H, d, J=6.96 Hz);
Mass (APCI): 367 $(M+H)^+$;
Anal. Calcd for $C_{20}H_{22}N_4OS$: C, 65.55; H, 6.05; N, 15.29.

Found: C, 65.55; H, 5.9; N, 15.30.

Example 36

Tert-butyl 4-([3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)pyrazolo[1,5-a]pyridin-2-yl]methylene)-1-piperidinecarboxylate
mp: 186.5-188°C (acetone-hexane);
IR (KBr): 1687, 1664, 1590 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.62 Hz), 1.48 (9H, s), 2.35-2.45 (2H, m), 2.65-2.75 (2H, m), 3.4-3.5 (2H, m), 3.5-3.6 (2H, m), 5.44 (1H, 7-plet, J=6.62 Hz), 6.46 (1H, br. s), 6.8-6.9 (1H, m), 6.97 (1H, d, J=9.61 Hz), 7.2-7.3 (1H, m), 7.55 (1H, d, J=9.61 Hz), 7.91 (1H, d, J=8.94 Hz), 8.45 (1H, d, J=6.95 Hz);
Mass (ESI): 921 $(2M+Na)^+$, 472 $(M+Na)^+$, 394.

Example 37

6-(2-[(2,2-Dimethyl-1,3-dioxan-5-ylidene)methyl]-pyrazolo[1,5-a]pyridin-3-yl)-2-isopropyl-3(2H)-pyridazinone
mp: 137-138.5°C (acetone-hexane)
IR (KBr): 1656, 1587 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.62 Hz), 1.48 (6H, s), 4.47 (2H, br. s), 4.96 (2H, br. s), 5.44 (1H, 7-plet, J=6.62 Hz), 6.46 (1H, br. s), 6.8-6.9 (1H, m), 7.00 (1H, d, J=9.58 Hz), 7.2-7.3 (1H, m), 7.50 (1H, d, J=9.58 Hz), 7.82 (1H, d, J=8.96 Hz), 8.44 (1H, d, J=6.97 Hz);
Mass (ESI): 783 $(2M+Na)^+$, 403 $(M+Na)^+$, 381 $(M+H)^+$.

Example 38

2-Isopropyl-6-(2-[(2,2,5,5-tetramethyldihydro-3(2H)-furanylidene)methyl]pyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (E- or Z-isomer)
mp: 204-206°C (acetone-hexane);
IR (KBr): 1660, 1590 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.31 (6H, s), 1.46 (6H, s), 1.47 (6H, d, J=6.62 Hz), 3.05 (2H, d, J=2.32 Hz), 5.45 (1H, 7-plet, J=6.62 Hz), 6.51 (1H, t, J=2.32 Hz), 6.8-6.9 (1H, m), 6.99 (1H, d, J=9.58 Hz), 7.2-7.3 (1H, m), 7.49 (1H, d, J=9.58 Hz), 7.80 (1H, d, J=8.93 Hz), 8.48 (1H, d, J=6.95 Hz);

Mass (APCI): 393 $(M+H)^+$.

Example 39

6-{2-[Dihydro-3(2H)-thienylidenemethyl]pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone (E,Z-mixture)

mp: 60-69°C;

IR (KBr): 1654, 1585 cm^{-1};

^1H NMR ($CDCl_3$, δ): 6.65 and 6.69 (vinylic proton);

Mass (APCI): 353 $(M+H)^+$.

Example 40

6-[2-(Bicyclo[2.2.1]hept-2-ylidenemethyl)pyrazolo-[1,5-a]pyridin-3-yl]-2-isopropyl-3(2H)-pyridazinone (E,Z-mixture)

IR (Neat): 1664, 1631, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 6.25 and 6.53 (vinylic proton);

Mass (APCI): 361 $(M+H)^+$.

Example 41

2-Isopropyl-6-[2-(tricyclo[3.3.1.$1^{3,7}$]dec-2-ylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone

mp: 96-101°C;

IR (KBr): 1664, 1590 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 1.7-2.0 (13H, m), 2.63 (1H, br. s), 3.26 (1H, br. s), 5.44 (1H, 7-plet, J=6.62 Hz), 6.75-6.9 (1H, m), 6.95 (1H, d, J=9.61 Hz), 7.15-7.3 (1H, m), 7.67 (1H, d, J=9.61 Hz), 7.92 (1H, d, J=8.92 Hz), 8.45 (1H, d, J=6.94 Hz);

Mass (APCI): 401 $(M+H)^+$.

Example 42

2-Isopropyl-6-[2-((E)-2-phenylethenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone

mp: 148.5-149.5°C (isopropyl ether);

IR (KBr): 1662, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.50 (6H, d, J=6.63 Hz), 5.47 (1H, 7-plet, J=6.63 Hz), 6.85-6.93 (1H, m), 7.03 (1H, d, J=9.57 Hz), 7.21-7.44 (5H, m), 7.51-7.67 (4H, m), 7.79 (1H, d, J=8.92 Hz), 8.51 (1H, d, J=6.94 Hz);

Mass (APCI): 357 $(M+H)^+$.

Example 43

6-{2-[(E)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)-ethenyl]pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone

mp: 181-182°C (isopropyl ether);

IR (KBr): 1658, 1583 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.49 (6H, d, J=6.63 Hz), 4.29 (4H, s), 5.46 (1H, 7-plet, J=6.63 Hz), 6.84-6.91 (2H, m), 6.99-7.29 (5H, m), 7.46-7.56 (2H, m), 7.78 (1H, d, J=8.93 Hz), 8.49 (1H, d, J=6.93 Hz);

Mass (APCI): 415 $(M+H)^+$.

Example 44

6-{2-[(E)-2-(1-Ethyl-1H-indol-3-yl)ethenyl]pyrazolo-[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone

mp: 83-85°C (isopropyl ether);

IR (KBr): 1658, 1626, 1587 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.50 (3H, t, J=7.26 Hz), 1.51 (6H, d, J=6.63 Hz), 4.20 (2H, q, J=7.26 Hz), 5.47 (1H, 7-plet, J=6.63 Hz), 6.81-6.89 (1H, m), 7.02 (1H, d, J=9.57 Hz), 7.17-7.41 (6H, m), 7.63 (1H, d, J=9.57 Hz), 7.74-7.83 (2H, m), 7.96 (1H, d, J=7.17 Hz), 8.50 (1H, d, J=6.93 Hz);

Mass (APCI): 424 $(M+H)^+$.

Example 45

2-Isopropyl-6-{2-[(E)-2-(2-quinolyl)ethenyl]pyrazolo-[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone

mp: 171-172°C (acetone-hexane);

IR (KBr): 1664, 1591 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.54 (6H, d, J=6.63 Hz), 5.49 (1H, 7-plet, J=6.63 Hz), 6.87-6.96 (1H, m), 7.06 (1H, d, J=9.55 Hz), 7.23-7.32 (1H, m), 7.42-7.89 (7H, m), 8.05 (1H, d, J=8.39 Hz), 8.23-8.13 (2H, m), 8.53 (1H, d, J=6.96 Hz);

Mass (ESI): 837 $(2M+Na)^+$, 430 $(M+Na)^+$, 408 $(M+H)^+$, 301.

Example 46

6-[2-((E)-2-Cyclohexylethenyl)pyrazolo[1,5-a]pyridin-

3-yl]-2-isopropyl-3(2H)-pyridazinone
mp: 90-92°C (isopropyl ether);
IR (KBr): 1662, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.0-1.9 (H, m), 1.47 (6H, d, J=6.63 Hz), 2.05-2.15 (1H, m), 5.44 (1H, 7-plet), 6.54-6.74 (2H, m), 6.79-6.87 (1H, m), 6.98 (1H, d, J=9.58 Hz), 7.17-7.27 (1H, m), 7.49 (1H, d, J=9.58 Hz), 7.79 (1H, d, J=8.92 Hz), 8.45 (1H, d, J=6.94 Hz);
Mass (APCI): 363 $(M+H)^+$.

Example 47

2-Isopropyl-6-{2-[(E)-2-(morpholinophenyl)ethenyl]-pyrazolo[1,5-a]pyridin-3-yl}-3(2H)-pyridazinone
mp: 210-211°C (methanol);
IR (KBr): 1662, 1599, 1589 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.39 (6H, d, J=6.61 Hz), 3.15-3.19 (2H, m), 3.71-3.77 (2H, m), 5.23 (1H, 7-plet, J=6.61 Hz), 6.93-7.07 (H, m), 7.23-7.54 (H, m), 7.75 (1H, d, J=9.62 Hz), 7.83 (1H, d, J=8.90 Hz), 8.75 (1H, d, J=6.88 Hz);
Mass (APCI): 442 $(M+H)^+$.

Example 48

To a solution of methyltriphenylphosphonium bromide (141.7 mg) in dimethyl sulfoxide (0.5 mL) was added potassium tert-butoxide (44.5 mg) at 10-15°C and the mixture was stirred at ambient temperature for an hour. To the reaction mixture, 3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)pyrazolo[1,5-a]pyridine-2-carbaldehyde (100.3 mg) was added and stirred at ambient temperature for 4 days. The mixture was poured into water, extracted with ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 1:5 v/v) to give 2-isopropyl-6-(2-vinylpyrazolo-[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone as a solid (16.1 mg).
mp: 129-131°C (hexane);
IR (KBr): 1664, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 5.44 (1H, 7-plet, J=6.64 Hz), 5.57 (1H, dd, J=1.68, 11.10 Hz), 6.20 (1H, dd, J=1.66, 17.53 Hz), 6.83-6.92 (1H, m), 6.98 (1H, dd, J=11.10, 17.52 Hz), 6.99 (1H, d, J=9.58 Hz), 7.20-7.48 (1H, m), 7.50 (1H, d, J=9.58 Hz), 7.78-7.84 (1H, m), 8.45-8.50 (1H, m);
Mass (APCI): 281 $(M+H)^+$;
Anal. Calcd for $C_{16}H_{16}N_4O \cdot 0.25H_2O$: C, 67.47; H, 5.84; N, 19.67.
Found: C, 67.70; H, 5.79; N, 19.45.

Example 49

A solution of 3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)pyrazolo[1,5-a]pyridine-2-carbaldehyde (43.3 mg) and 1-(triphenylphosphoranylidene)acetone (49.1 mg) in a mixture of tetrahydrofuran (0.5 mL) and ethyl acetate (0.5 mL) was stirred at ambient temperature for 4 days. An insoluble material was collected by filtration and dried under reduced pressure to give 2-isopropyl-6-[2-((1E)-3-oxo-1-butenyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (38.4 mg).
mp: 186-188°C;
IR (KBr): 1664, 1656, 1587 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.38 (6H, d, J=6.62 Hz), 2.37 (3H, s), 5.27 (1H, 7-plet, J=6.62 Hz), 7.01 (1H, d, J=16.14 Hz), 7.07 (1H, d, J=9.62 Hz), 7.10-7.18 (1H, m), 7.40-7.49 (1H, m), 7.79 (1H, d, J=9.62 Hz), 7.86 (1H, d, J=16.14 Hz), 8.82 (1H, d, J=6.98 Hz);
Mass (APCI): 323 $(M+H)^+$.

Example 50

Urea hydrogen peroxide addition compound (42.3 mg) was added to a solution of 2-isopropyl-6-[2-(tetrahydro-4H-thiopyran-4-ylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (80.2 mg) in glacial acetic acid (0.16 mL). The mixture was heated at 80-85°C for 2 hours. After cooling, 2% aqueous sodium thiosulfate solution was added. The mixture was extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure

to give a residue. The residue was purified by preparative TLC on silica gel (ethyl acetate only) to give 6-{2-[(1,1-dioxo-1λ⁶-tetrahydro-4H-thiopyran-4-ylidene)methyl]pyrazolo-[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone as a solid (45.6 mg).

mp: 200.5-202.5°C (hexane);

IR (KBr): 1662, 1590 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.62 Hz), 2.9-3.0 (2H, m), 3.1-3.2 (4H, m), 3.35-3.45 (2H, m), 5.44 (1H, 7-plet, J=6.61 Hz), 6.63 (1H, s), 6.85-6.95 (1H, m), 7.01 (1H, d, J=9.59 Hz), 7.25-7.35 (1H, m), 7.48 (1H, d, J=9.59 Hz), 7.85 (1H, d, J=8.96 Hz), 8.45 (1H, d, J=6.98 Hz);

Mass (APCI): 399 $(M+H)^+$.

Example 51

In the presence of Nafion® NR50 (50 mg), a solution of 6-{2-[(2,2-dimethyl-1,3-dioxan-5-ylidene)methyl]-pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone (104.7 mg) in a mixture of water (0.2 mL) and dioxane (1 mL) was refluxed for 3 hours. The resin was filtered off and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (ethyl acetate only) to give 6-{2-[3-hydroxy-2-(hydroxymethyl)-1-propenyl]pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone as a solid (74.8 mg).

mp: 164.5-166.5°C (acetone);

IR (KBr): 1660, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.63 Hz), 2.02 (1H, br. s), 4.31 (2H, d, J=7.11 Hz), 4.44 (2H, br. s), 4.98 (1H, t, J=7.27 Hz), 5.44 (1H, 7-plet, J=6.62 Hz), 6.88 (1H, s), 6.85-6.95 (1H, m), 7.01 (1H, d, J=9.58 Hz), 7.25-7.35 (1H, m), 7.51 (1H, d, J=9.56 Hz), 7.88 (1H, d, J=8.95 Hz), 8.46 (1H, d, J=6.95 Hz);

Mass (APCI): 341 $(M+H)^+$, 323.

Example 52

A solution of tert-butyl 4-{[3-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)pyrazolo[1,5-a]pyridin-2-

yl]methylene}-1-piperidinecarboxylate (133.6 mg) in a mixture of 4N hydrochloric acid (1 mL) and dioxane (2 mL) was stirred at ambient temperature for 3 hours. The mixture was poured into saturated aqueous sodium hydrogencarbonate solution, extracted with chloroform, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was triturated with isopropyl ether, collected by filtration, and dried under reduced pressure to give 2-isopropyl-6-[2-(4-piperidinylidenemethyl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (52.8 mg).

mp: 120-123°C (isopropyl ether);

IR (KBr): 1662, 1590 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.62 Hz), 2.4-2.5 (2H, m), 2.6-2.7 (2H, m), 2.85-2.95 (2H, m), 3.0-3.1 (2H, m), 5.44 (1H, 7-plet, J=6.62 Hz), 6.38 (1H, s), 6.8-6.9 (1H, m), 6.96 (1H, d, J=9.61 Hz), 7.2-7.3 (1H, m), 7.59 (1H, d, J=9.61 Hz), 7.92 (1H, d, J=8.95 Hz), 8.45 (1H, d, J=6.96 Hz);

Mass (APCI): 350 $(M+H)^+$.

Example 53

To a solution of 2-isopropyl-6-[2-(4-piperidinylidenemethyl)pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (55.3 mg) in a mixture of triethylamine (0.2 mL) and dichloromethane (0.5 mL), acetic anhydride (0.2 mL) was added dropwise under ice-cooling and the mixture was stirred at the same temperature for an hour and at ambient temperature for 2 hours. The mixture was concentrated under reduced pressure and purified by preparative TLC on silica gel (methanol-chloroform 5:95 v/v) to give 6-{2-[(1-acetyl-4-piperidinylidene)methyl]pyrazolo[1,5-a]pyridin-3-yl}-2-isopropyl-3(2H)-pyridazinone as an amorphous (60.2 mg).

mp: 52-57°C;

IR (KBr): 1652, 1585 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.63 Hz), 2.14 and 2.16 (3H, each s), 2.4-2.55 (2H, m), 2.7-2.85 (2H, m), 3.45-3.55 (1H, m), 3.55-3.7 (2H, m), 3.7-3.8 (1H, m), 5.44 (1H, 7-

plet, J=6.62 Hz), 6.50 (1H, br. s), 6.8-6.9 (1H, m), 6.95-7.05 (1H, m), 7.2-7.3 (1H, m), 7.5-7.6 (1H, m), 7.85-7.95 (1H, m), 8.4-8.5 (1H, m);
Mass (APCI): 392 $(M+H)^+$.

Preparation 73

Trifluoromethanesulfonic anhydride (3.55 mL) was added dropwise to a solution of 3,6-dihydroxypyridazine (2.25 g) in pyridine (50 mL) under ice-cooling. The mixture was stirred under ice-cooling for one hour and at ambient temperature for 2 hours. After addition of methanol (1 mL) under ice-cooling, pyridine was evaporated under reduced pressure to give a syrup. The syrup was dissolved in ethyl acetate, washed with water, 1N hydrochloric acid, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 60:40 and 40:60 v/v) to give 6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate as a solid (4.10 g).
mp: 130-131.5°C (acetone-hexane);
IR (KBr): 3080, 2985, 2881, 1703, 1641, 1597 cm^{-1};
^1H NMR (DMSO-d_6, δ): 7.18 (1H, d, J=10.05 Hz), 7.76 (1H, d, 10.05 Hz), 13.27 (1H, s);
Mass (ESI): 243 $(M-H)^-$;
Anal. Calcd for $C_5H_3F_3N_2O_4S$: C, 24.60; H, 1.24; N, 11.47;
Found: C, 24.63; H, 1.16; N, 11.43.

Preparation 74

In the presence of bis(triphenylphosphine)palladium(II) dichloride (702 mg) and copper(I) iodide (190 mg), a solution of triethylamine (20.7 mL) in dioxane (10 mL) was added dropwise to a mixture of 6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate (30.20 g), 2-methyl-3-butyn-2-ol (12.49 g) in dioxane (120 mL) at 75-80°C for 0.5 hour. The mixture was stirred at 75-80°C for 2 hours. After cooling, water and chloroform were added to the mixture. The organic layer was washed with

brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane-ethyl acetate 20:80 v/v) to give 6-(3-hydroxy-3-methyl-1-butynyl)-3(2H)-pyridazinone as a solid (13.35 g).
mp: 168-169°C (acetone-hexane);
IR (KBr): 1670, 1649, 1583 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.45 (6H, s), 5.59 (1H, br.s), 6.86 (1H, d, J=9.75 Hz), 7.38 (1H, d, J=9.75 Hz), 13.22 (1H, br.s);
Mass (APCI): 179 $(M+H)^+$, 161;
Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72;
Found C: 60.68; H: 6.03; N: 15.47.

Preparation 75

A mixture of 6-(3-hydroxy-3-methyl-1-butynyl)-3(2H)-pyridazinone (5.00 g), 1-aminopyridinium iodide (3.12 g) and potassium carbonate (15.51 g) in dimethylformamide (30 mL) was stirred at 100-105°C for 0.5 hour. To the mixture, 1-aminopyridinium iodide (3.12 g) was added and the mixture was stirred at 100-105°C for 0.5 hour. Furthermore, 1-aminopyridinium iodide (3.12 g) was added to the mixture 4 times and the mixture was stirred at the same temperature for 6 hours. After cooling, the mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol-chloroform 3:97 v/v) to give 6-[2-(1-hydroxy-1-methylethyl)-pyrazolo[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone as a crude solid. The solid was suspended in hot methanol. After cooling, the solid was collected by filtration to give a pure compound.
mp: 252-254°C (methanol);
IR (KBr): 3365, 1655, 1585 cm^{-1};
^1H NMR (DMSO-d_6, δ): 1.57 (6H, s), 5.40 (1H, s), 6.86-6.98 (2H, m), 7.25-7.33 (1H, m), 7.67 (1H, d, J=8.98 Hz), 7.96 (1H, d, J=9.84 Hz), 8.67 (1H, d, J=6.96 Hz), 13.02 (1H, s);
Mass (ESI): 293 $(M+Na)^+$, 253;
Anal. Calcd for $C_{14}H_{14}N_4O_2 \cdot 0.1H_2O$ C: 61.80; H: 5.26; N:

20.59;

Found: C, 61.78; H, 5.12; N, 20.58.

Example 54

A mixture of 6-[2-(1-hydroxy-1-methylethyl)pyrazolo-[1,5-a]pyridin-3-yl]-3(2H)-pyridazinone (102 mg) and methanesulfonic acid (13 mg) in xylene (2 mL) was refluxed for 30 hours. Chloroform (10 mL) was added to the mixture. The solution was washed with aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (ethyl acetate) to give 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone as a solid (66 mg).

mp: 200-201.5°C (methanol);

IR (KBr): 1680, 1662, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 2.25 (3H, s), 5.29 (1H, br.s), 5.44 (1H, br.s), 6.82-6.91 (1H, m), 6.98 (1H, d, J=9.84 Hz), 7.20-7.29 (1H, m), 7.62 (1H, d, J=9.84 Hz), 7.93 (1H, d, J=9.00 Hz), 8.45 (1H, d, J=6.94 Hz), 11.30 (1H, br.s);

Mass (ESI): 275 $(M+Na)^+$;

Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.66; H, 4.79; N, 22.21;

Found C, 66.43; H, 4.77; N, 22.18.

Example 55

To a solution of 6-(2-isopropenylpyrazolo[1,5-a]-pyridin-3-yl)-3(2H)-pyridazinone (63 mg) in dimethylformamide (0.2 mL) was added sodium hydride (60 % in oil, 11 mg) and the mixture was stirred at 50-55°C for one hour. Iodomethane (0.062 mL) was added to the mixture and the mixture was stirred at ambient temperature for 18 hours. The mixture was poured into ethyl acetate, washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC on silica gel (ethyl acetate) to give 6-(2-isopropenyl-pyrazolo[1,5-a]pyridin-3-yl)-2-methyl-3(2H)-pyridazinone as a solid (55 mg).

m.p.: 98-100°C (diisopropyl ether-hexane);

IR (KBr): 1668, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 2.24 (3H, br.s), 3.89 (3H, s), 5.29 (1H, br.s), 5.42 (1H, br.s), 6.81-6.90 (1H, m), 6.94 (1H, d, J=9.64 Hz), 7.21-7.30 (1H, m), 7.53 (1H, d, J=9.64 Hz), 7.87-7.93 (1H, m), 8.42-8.48 (1H, m);

Mass (APCI): 267$(M+H)^+$;

Anal. Calcd for $C_{15}H_{14}N_4O \cdot 0.1H_2O$: C, 67.20; H, 5.34; N, 20.90;

Found: C, 67.35; H, 5.38; N, 20.82.

Example 56

2-Ethyl-6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone was prepared as a solid (62 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and iodoethane (0.0399 mL) in a similar manner to Example 55.

m.p.: 102.5-103.5°C (diisopropyl ether-hexane);

IR (KBr): 1657, 1589 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.49 (3H, t, J=7.18 Hz), 2.24 (3H, br.s), 4.32 (2H, q, J=7.18 Hz), 5.30 (1H, br.s), 5.41 (1H, br.s), 6.85-6.91 (1H, m), 6.92 (1H, d, J=9.62 Hz), 7.21-7.30 (1H, m), 7.51 (1H, d, J=9.62 Hz), 7.85-7.92 (1H, m), 8.42-8.48 (1H, m);

Mass (APCI): 281 $(M+H)^+$;

Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N,19.99;

Found: C,68.74; H,5.73; N, 20.05.

Example 57

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-propyl-3(2H)-pyridazinone was prepared as a solid (64 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and 1-iodopropane (0.0487 mL) in a similar manner to Example 55.

m.p.: 76-78°C (hexane);

IR (KBr): 1660, 1591 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.04 (3H, t, J=7.42 Hz), 1.95 (2H, m), 2.24 (3H, br.s), 4.23 (2H, t, J=7.39 Hz), 5.29 (1H, br.s), 5.41 (1H, br.s), 6.81-6.90 (1H, m), 6.92 (1H, d, J=9.64 Hz),

7.20-7.30 (1H, m), 7.50 (1H, d, J=9.64 Hz), 7.83-7.90 (1H, m), 8.42-8.47 (1H, m);
Mass (APCI): 295(M+H)$^+$;
Anal. Calcd for $C_{17}H_{18}N_4O \cdot 0.1H_2O$: C, 68.95; H, 6.19; N, 18.92;
Found: C, 68.81; H, 6.18; N, 18.82.

Example 58

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-isopropyl-3(2H)-pyridazinone was prepared as a solid (69 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and 2-iodopropane (0.025 mL) in a similar manner to Example 55.
mp: 89-90°C (hexane);
IR (KBr): 1679, 1594 cm^{-1};
Mass (APCI): 295(M+H)$^+$;
^{1}H NMR ($CDCl_3$, δ): 1.47 (6H, d, J=6.64 Hz), 2.24 (3H, s), 5.27 (1H, br.s), 5.3-5.5 (2H, m), 6.8-6.9 (1H, m), 6.91 (1H, d, J=9.59 Hz), 7.26 (1H, d, J=7.87 Hz), 7.50 (1H, d, J=9.60 Hz), 7.90 (1H, d, J=8.95 Hz), 8.45 (1H, d, J=6.97 Hz);
Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03;
Found: C, 69.43; H, 6.19; N, 19.00.

Example 59

2-Allyl-6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone was prepared as a solid (60 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and allyl bromide (0.0432 mL) in a similar manner to Example 55.
mp: 64-65°C (diisopropyl ether-hexane);
IR (KBr): 1668, 1591 cm^{-1};
^{1}H NMR ($CDCl_3$, δ): 2.24 (3H, br.s), 4.85-4.90 (2H, m), 5.29-5.44 (4H, m), 6.01-6.22 (1H, m), 6.70-6.90 (1H, m), 6.94 (1H, d, J=9.65 Hz), 7.20-7.29 (1H, m), 7.53 (1H, d, J=9.65 Hz), 7.86-7.92 (1H, m), 8.42-8.47 (1H, m);
Mass (APCI): 293(M+H)$^+$.

Example 60

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(2-propynyl)-3(2H)-pyridazinone (26 mg, as a solid) and 2-(1-ethynyl-3-butynyl)-6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (6 mg, as a syrup) were prepared, from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and propargyl bromide (0.0445 mL) in a similar manner to Example 55.

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(2-propynyl)-3(2H)-pyridazinone
mp: 103.5-105°C (acetone-hexane);
IR (KBr): 1668, 1591 cm^{-1};
^{1}H NMR ($CDCl_3$, δ): 2.25 (3H, br.s), 2.41 (1H, t, J=2.52 Hz), 5.04 (2H, d, J=2.52 Hz), 5.30 (1H, br.s), 5.44 (1H, br.s), 6.85-6.92 (1H, m), 6.95 (1H, d, J=9.72 Hz), 7.23-7.32 (1H, m), 7.57 (1H, d, J=9.72 Hz), 8.02-8.29 (1H, m), 8.42-8.48 (1H, m);
Mass (APCI): 291(M+H)$^+$.

2-(1-Ethynyl-3-butynyl)-6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone
^{1}H NMR ($CDCl_3$, δ): 2.04 (1H, t, J=2.58 Hz), 2.26 (3H, br.s), 2.50 (1H, d, J=2.36 Hz), 2.91-3.15 (2H, m), 5.30 (1H, br.s), 5.44 (1H, br.s), 6.17 (1H, dt, J=2.36,7.45 Hz), 6.83-6.92 (1H, m), 6.93 (1H, d, J=9.70 Hz), 7.22-7.60 (1H, m), 7.57 (1H, d, J=9.70 Hz), 8.12-8.17 (1H, m), 8.43-8.47 (1H, m);
Mass (APCI): 329 (M+H)$^+$, 253;
Mass (ESI): 680 (2M+Na)$^+$, 351(M+Na)$^+$, 329(M+H)$^+$.

Example 61

2-Benzyl-6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone was prepared as a solid (47 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and benzyl bromide (0.0356 mL) in a similar manner to Example 55.
mp: 165-167°C (methanol-diisopropyl ether);
IR (KBr): 1662, 1589 cm^{-1};
^{1}H NMR ($CDCl_3$, δ): 2.21-2.23(3H, m), 5.28 (1H, br.s), 5.40 (1H, br.s), 5.43 (2H, s), 6.77-6.87 (1H, m), 6.95 (1H, d, J=9.60 Hz), 7.07-7.17 (1H, m), 7.34-7.54 (7H, m), 8.38-8.44

(1H, m);
Mass (APCI): 343 $(M+H)^+$;
Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N,16.36;
Found: C, 73.74; H, 5.32; N, 16.42.

Example 62

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(2-methoxyethyl)-3(2H)-pyridazinone was prepared as a syrup (65 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and 2-chloroethyl methyl ether (0.0456 mL) in a similar manner to Example 55.
IR (Neat): 1664, 1591cm^{-1};
^1H NMR ($CDCl_3$, δ): 2.24 (3H, br.s), 3.42 (3H, s), 3.88 (2H, t, J=5.59 Hz), 4.47 (2H, t, J=5.59 Hz), 5.30 (1H, br.s), 5.42 (1H, br.s), 6.81-6.89 (1H, m), 6.93 (1H, d, J=9.68 Hz), 7.20-7.29 (1H, m), 7.52 (1H, d, J=9.68 Hz), 7.93-7.99 (1H, m), 8.41-8.47 (1H, m);
Mass (APCI): 311$(M+H)^+$, 279.

Example 63

2-(Cyclopropylmethyl)-6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone was prepared as a syrup (65 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and (bromomethyl)cyclopropane (0.0291 mL) in a similar manner to Example 55.
IR (Neat): 1664, 1589 cm^{-1};
^1H NMR ($CDCl_3$, δ): 0.45-0.68 (4H, m), 1.40-1.57 (1H, m), 2.24 (3H, br.s), 4.12 (2H, d, J=7.18 Hz), 5.30 (1H, br.s), 5.42 (1H, br.s), 6.85-6.90 (1H, m), 6.94 (1H, d, J=9.60 Hz), 7.20-7.29 (1H, m), 7.51 (1H, d, J=9.60 Hz), 7.86-7.92 (1H, m), 8.42-8.45 (1H, m);
Mass (APCI): 307$(M+H)^+$.

Example 64

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(2-oxopropyl-3(2H)-pyridazinone was prepared as a solid (231 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (253 mg) and 1-chloroacetone (0.0958 mL) in a similar manner to Example 55.

mp: 156.5-157.5°C (acetone);
IR (KBr): 1732, 1666, 1595 cm^{-1};
^1H NMR ($CDCl_3$, δ): 2.25 (3H, br.s), 2.31 (3H, s), 5.05 (2H, s), 5.30 (1H, br.s), 5.42 (1H, br.s), 6.80-6.89 (1H, m), 6.96 (1H, d, J=9.70 Hz), 7.18-7.27 (1H, m), 7.54 (1H, d, J=9.70 Hz), 7.76-7.82 (1H, m), 8.41-8.46 (1H, m);
Mass (APCI): 309$(M+H)^+$;
Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17;
Found: C, 66.17; H, 5.26; N, 18.17.

Example 65

Methyl [3-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-6-oxo-1(6H)-pyridazinyl]acetate was prepared as a solid (141 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (126 mg) and methyl bromoacetate (0.0567 mL) in a similar manner to Example 55.
mp: 77.5-78.5°C (acetone-hexane);
IR (KBr): 1755, 1672, 1593 cm^{-1};
^1H NMR ($CDCl_3$, δ): 2.25 (3H, br.s), 3.83 (3H, s), 5.00 (2H, s), 5.30 (1H, br.s), 5.43 (1H, br.s), 6.81-6.90 (1H, m), 6.96 (1H, d, J=9.70 Hz), 7.20-7.29 (1H, m), 7.55 (1H, d, J=9.70 Hz), 7.81-7.88 (1H, m), 8.41-8.47 (1H, m);
Mass (APCI): 325 $(M+H)^+$, 293.

Example 66

2-(1,3-Dioxolan-2-ylmethyl)-6-(2-isopropenylpyrazolo-[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone was prepared as a syrup (73 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and 2-(bromomethyl)-1,3-dioxolane (0.031 mL) in a similar manner to Example 55.
IR (Neat): 1664, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 2.24 (3H, br.s), 3.95-4.11 (4H, m), 4.43 (1H, d, J=4.82 Hz), 5.30 (1H, br.s), 5.42 (1H, br.s), 5.49 (1H, t, J=4.82 Hz), 6.70-6.90 (1H, m), 6.94 (1H, d, J=9.65 Hz), 7.24-7.30 (1H, m), 7.52 (1H, d, J=9.65 Hz), 7.98-8.04 (1H, m), 8.41-8.47 (1H, m);
Mass (APCI): 339 $(M+H)^+$.

Example 67

6-(2-Isopropenylpyrazolo[1,5-a]pyridin-3-yl)-2-(1,2,4-oxadiazol-3-ylmethyl)-3(2H)-pyridazinone was prepared as a solid (44 mg), from 6-(2-isopropenylpyrazolo[1,5-a]pyridin-3-yl)-3(2H)-pyridazinone (63 mg) and 3-(chloromethyl)-1,2,4-oxadiazole (36 mg) in a similar manner to Example 55.

mp: 144-146°C (acetone-hexane);

IR (KBr): 1672, 1595, 1529 cm^{-1};

^1H NMR ($CDCl_3$, δ): 2.24 (3H, br.s), 5.29 (1H, br.s), 5.44 (1H, br.s), 5.64 (2H, s), 6.80-6.89 (1H, m), 6.98 (1H, d, J=9.72 Hz), 7.18-7.26 (1H, m), 7.59 (1H, d, J=9.72 Hz), 7.80-7.86 (1H, m), 8.40-8.46 (1H, m), 8.74 (1H, s);

Mass (APCI): 335 $(M+H)^+$, 292, 265;

Anal. Calcd for $C_{17}H_{14}N_6O_2$: C,61.07; H,4.22; N,25.14;
Found: C,61.14; H,4.21; N,24.99.

Preparation 76

6-[2-(1-Hydroxy-1-methylethyl)pyrazolo[5,1-a]-isoquinolin-1-yl]-2-isopropyl-3(2H)-pyridazinone was prepared as a solid (148 mg), from 6-(3-hydroxy-3-methyl-1-butynyl)-2-isopropyl-3(2H)-pyridazinone (225 mg) and 2-aminoisoquinolinium iodide (136 mg x 4) in a similar manner to Preparation 75.

mp: 194-196°C (acetone-hexane);

IR (KBr): 3350, 1655, 1591 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.43 (6H, d, J=6.66 Hz), 1.62 (6H, s), 3.63 (1H, br.s), 5.47 (1H, 7-plet, J=6.66 Hz), 7.03-7.04 (2H, m), 7.34-7.61 (4H, m), 7.75 (1H, d, J=8.00 Hz), 8.22 (1H, d, J=7.38 Hz);

Mass (APCI): 363 $(M+H)^+$, 345.

Example 68

A mixture of 6-[2-(1-hydroxy-1-methylethyl)pyrazolo-[5,1-a]isoquinolin-1-yl]-2-isopropyl-3(2H)-pyridazinone (100 mg) and methanesulfonic acid (10 mg) in toluene (2 mL) was refluxed for 30 hours. Chloroform was added to the mixture. The solution was washed with aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced presseure to give a residue. The

residue was purified by preparative TLC on silica gel (hexane-ethyl acetate 50:50 v/v) to give 6-(2-isopropenylpyrazolo[5,1-a]isoquinolin-1-yl)-2-isopropyl-3(2H)-pyridazinone as a solid (74 mg).

mp: 117.5-118.5°C (diisopropyl ether-hexane);

IR (KBr): 1666, 1593 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.41 (6H, d, J=6.64 Hz), 2.18-2.20 (3H, m), 5.12-5.14 (1H, m), 5.24-5.26 (1H, m), 5.48 (1H, 7-plet, J=6.64 Hz), 7.00-7.07 (2H, m), 7.27 (1H, d, J=9.42 Hz), 7.37-7.43 (1H, m), 7.49-7.57 (1H, m), 7.73 (1H, d, J=7.82 Hz), 7.79 (1H, d, J=8.12 Hz), 8.23 (1H, d, J=7.36 Hz);

Mass (APCI): 345$(M+H)^+$;

Anal. Calcd for $C_{21}H_{20}N_4O$: C, 73.23; H, 5.85; N, 16.27;
Found: C, 73.06; H, 5.83; N, 16.25.

Preparation 77

6-[2-(1-Hydroxycyclobutyl)pyrazolo[5,1-a]isoquinolin-1-yl]-2-isopropyl-3(2H)-pyridazinone was prepared as a solid (159 mg), from 6-[2-(1-hydroxycyclobutyl)-1-ethynyl]-2-isopropyl-3(2H)-pyridazinone (235 mg) and 2-aminoisoquinolinium iodide (136 mg x 4) in a similar manner to Preparation 75.

mp: 186-187°C (acetone);

IR (KBr): 3384, 1655, 1591 cm^{-1};

^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.70 Hz), 1.64-1.74 (1H, m), 1.92-2.10 (1H, m), 2.25-2.42 (2H, m), 2.59-2.71 (2H, m), 4.03 (1H, s), 5.47 (1H, 7-plet, J=6.70 Hz), 7.06 (1H, d, J=9.50 Hz), 7.08 (1H, d, J=7.42 Hz), 7.42-7.62 (3H, m), 7.74-7.83 (2H, m), 8.26 (1H, d, J=7.36);

Mass (APCI): 375 $(M+H)^+$, 305.

Example 69

6-[2-(1-Cyclobuten-1-yl)pyrazolo[5,1-a]isoquinolin-1-yl]-2-isopropyl-3(2H)-pyridazinone was prepared as a solid (37 mg), from 6-[2-(1-hydroxycyclobutyl)pyrazolo[5,1-a]-isoquinolin-1-yl]-2-isopropyl-3(2H)-pyridazinone (100 mg) in a similar manner to Example 54.

mp: 82-85°C (acetone-diisopropyl ether);

IR (KBr): 1660, 1591 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.42 (6H, d, J=6.64 Hz), 2.57-2.62 (2H, m), 2.89-2.96 (2H, m), 5.47 (1H, 7-plet, J=6.64 Hz), 5.99 (1H, t, J=1.18 Hz), 7.02-7.07 (2H, m), 7.32-7.58 (3H, m), 7.70-7.77 (2H, m), 8.24 (1H, d, J=7.38 Hz);
Mass (APCI): 357$(M+H)^+$.

Preparation 78

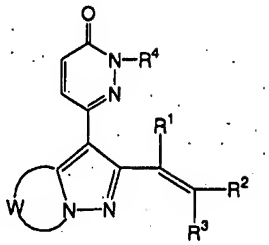
6-[2-(1-Hydroxy-1-methylethyl)pyrazolo[1,5-a]pyrazin-3-yl]-2-isopropyl-3(2H)-pyridazinone was prepared as a solid (211 mg), from 6-(3-hydroxy-3-methyl-1-butynyl)-2-isopropyl-3(2H)-pyridazinone (664 mg) and 1-aminopyrazin-1-ium iodide (335 mg x 8) in a similar manner to Preparation 75.
mp: 162-164.5°C (acetone-hexane);
IR (KBr): 1647, 1579 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.46 (6H, d, J=6.70 Hz), 1.72 (6H, s), 4.55 (1H, s), 5.48 (1H, 7-plet, J=6.71 Hz), 7.09 (1H, d, J=9.60 Hz), 7.70 (1H, d, J=9.60 Hz), 7.97 (1H, d, 4.72 Hz), 8.37 (1H, dd, J=1.44, 4.70 Hz), 9.11 (1H, d, J=1.44 Hz);
Mass (APCI): 314 $(M+H)^+$, 254;
Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35;
Found: C, 61.02; H, 6.26; N, 22.57.

Example 70

6-(2-Isopropenylpyrazolo[1,5-a]pyrazin-3-yl)-2-isopropyl-3(2H)-pyridazinone was prepared as a syrup (30 mg) which was solidified on standing at ambient temperature, from 6-[2-(1-hydroxy-1-methylethyl)pyrazolo[1,5-a]pyrazin-3-yl]-2-isopropyl-3(2H)-pyridazinone (95 mg) in a similar manner to Example 54.
mp: 129-130°C;
IR (KBr): 1662, 1595 cm^{-1};
^1H NMR ($CDCl_3$, δ): 1.48 (6H, d, J=6.64 Hz), 2.26 (3H, t, J=1.18 Hz), 5.33 (1H, s), 5.44 (1H, 7-plet, J=6.64 Hz), 5.47-5.50 (1H, m), 6.95 (1H, d, J=9.64 Hz), 7.55 (1H, d, 9.64 Hz), 7.97 (1H, d, J=4.72 Hz), 8.35 (1H, dd, J=1.44, 4.72 Hz), 9.38 (1H, d, 1.44 Hz);
Mass (APCI): 296 $(M+H)^+$, 254.

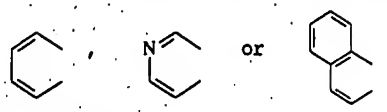
CLAIMS

1. A compound of the following formula (I):



(I)

wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen or a suitable substituent,
in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12) which is optionally interrupted by heteroatom(s) and optionally having suitable substituent(s); and

W is 

or a salt thereof.

2. The compound of claim 1, wherein
R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxy(lower)alkyl, cycloalkyl, acyl, aryl or heteroaryl,
in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12), at least one CH_2 of which is (are) optionally replaced by O, S, SO_2 or optionally protected imino, and optionally having suitable substituent(s), or R^2 and R^3 together may form bicycloalkylidene or tricycloalkylidene; and
R^4 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkadiynyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl(lower)alkyl, heterocyclic(lower)alkyl, lower

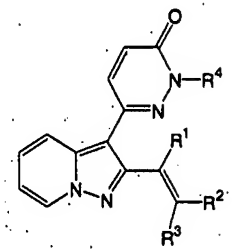
alkoxy(lower)alkyl or acyl(lower)alkyl,
or a salt thereof.

3. The compound of claim 2, wherein
R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxymethyl, cycloalkyl, acetyl, phenyl, benzodioxanyl, indolyl optionally having lower alkyl, quinolyl or morpholinophenyl,
in which R^1 and R^2 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 10, one CH_2 of which is optionally replaced by O or S and optionally having lower alkyl),
in which R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 3 to 12, at least one CH_2 of which is(are) optionally replaced by O, S, SO_2, NH, $N(COCH_3)$ or NBoc and optionally having lower alkyl), bicycloalkylidene or tricycloalkylidene; and
R^4 is lower alkyl, lower alkenyl, lower alkynyl, lower alkadiynyl, lower cycloalkyl, lower cycloalkyl(lower)alkyl, phenyl(lower)alkyl, dioxolanyl(lower)alkyl, oxadiazolyl(lower)alkyl, lower alkoxy(lower)alkyl, lower alkanoyl(lower)alkyl, lower alkoxycarbonyl(lower)alkyl, or a salt thereof.

4. The compound of claim 3, wherein
R^1 and R^2 are each independently hydrogen or lower alkyl,
in which R^1 and R^2 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 10, one CH_2 of which is optionally replaced by O or S and optionally having lower alkyl);
R^3 is hydrogen, lower alkyl, hydroxymethyl, cycloalkyl, acetyl, phenyl, benzodioxanyl, indolyl optionally having lower alkyl, quinolyl or morpholinophenyl,
in which R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 3 to 12, at least one CH_2 is(are) optionally replaced by O, S, SO_2, NH, $N(COCH_3)$ or NBoc and optionally having lower alkyl), bicycloheptylidene

or tricyclodecylidene;
R^4 is methyl, ethyl, propyl, isopropyl, allyl, propynyl, ethynylbutynyl, cyclopropylmethyl, benzyl, dioxolanylmethyl, oxadiazolylmethyl, methoxyethyl, acetonyl or methoxycarbonylmethyl,
or a salt thereof.

5. The compound of claim 1 represented by the following formula (I'):



(I')

wherein
R^1, R^2, R^3 and R^4 are each independently hydrogen or a suitable substituent,
in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12), which is optionally interrupted by heteroatom(s), and optionally having suitable substituent(s);
or a salt thereof.

6. The compound of claim 5, wherein
R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxy(lower)alkyl, cycloalkyl, acyl, aryl or heteroaryl,
in which R^1 and R^2 together or R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 1 to 12), at least one CH_2 of which is optionally replaced by O, S, SO_2 or optionally protected imino, and optionally having suitable substituent(s), or
R^2 and R^3 together may form bicycloalkylidene or tricycloalkylidene; and

R^4 is hydrogen, lower alkyl, cycloalkyl or cycloalkyl(lower)alkyl whose CH_2 is optionally replaced by O, NH, S or SO_2,
or a salt thereof.

7. The compound of claim 6, wherein
R^1, R^2 and R^3 are each independently hydrogen, lower alkyl, hydroxymethyl, cycloalkyl, acetyl, phenyl, benzodioxanyl, indolyl optionally having lower alkyl, quinolyl or morpholinophenyl,
in which R^1 and R^2 together may form $-(CH_2)_n-$ (wherein n is an integer of 2 to 6, and one CH_2 of which is optionally replaced by O or S and optionally having lower alkyl), or
in which R^2 and R^3 together may form $-(CH_2)_n-$ (wherein n is an integer of 3 to 7, and at least one CH_2 of which is optionally replaced by O, S, SO_2, NH, $N(COCH_3)$ or NBoc and optionally having lower alkyl), bicycloalkylidene or tricycloalkylidene; and
R^4 is isopropyl,
or a salt thereof.

8. A pharmaceutical composition comprising any of the compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

9. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout,

hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris, which comprises administering any of the compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof to a human being or an animal.

10. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, Meniere's syndrome and cerebral infarction, which comprises administering any of the compound of claims 1 to 7 or a pharmaceutically acceptable salt thereof to a human being or an animal.

11. The compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof for use as a medicament.

12. The compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof for use as an adenosine antagonist.

13. The compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof for use as an A_1 receptor and A_2 receptor dual antagonist.

14. A process for preparing a pharmaceutical composition which comprises admixing any of the compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

15. Use of any of the compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the therapy of diseases

on which an adenosine antagonist is therapeutically effective.

16. A method for evaluation of adenosine antagonism which comprises use of any of the compound of claim 1 to 7 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/06671

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D487/04 A61K31/501 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 24742 A (KURODA SATORU ;AKAHANE ATSUSHI (JP); ITANI HIROMICHI (JP); FUJISAW) 4 May 2000 (2000-05-04) cited in the application claims 1,7; table 1	1-16
X	WO 01 40230 A (TABUCHI SEIICHIRO ;KURODA SATORU (JP); TADA MIHO (JP); AKAHANE ATS) 7 June 2001 (2001-06-07) claims 1,11; table 1	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2002	09/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/06671

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0024742 A	04-05-2000	WO 0024742 A1	04-05-2000
WO 0140230 A	07-06-2001	AU 1309301 A	12-06-2001
		WO 0140230 A1	07-06-2001